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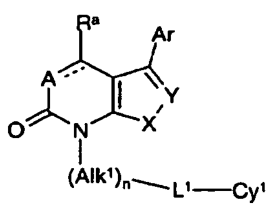
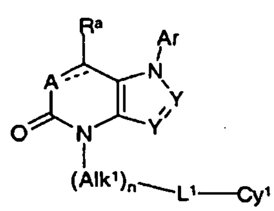


(1a)



(1b)

(57) Abstract: Compounds of formulae (1 a) and (1 b) are described: in which the dashed line represents an optional bond; A is a -N= atom or a -N(R^b)-, -C(R^b)= or -C(R^b)(R^C)- group; R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C^{1-6}alkyl group; X is an -O- or -S- atom or -NH- group or substituted N atom; each Y is independently a N atom or CH group or substituted C atom; n is zero or the integer 1; Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain L^1 is a covalent bond or a linker atom or group; Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group; Ar is an optionally substituted aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof; The compounds are potent inhibitors of p38 kinase and are use in the prophylaxis or treatment of p38 kinase mediated diseases or disorders, such as rheumatoid arthritis.

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BICYCLIC OXOPYRIDINE AND OXOPYRIMIDINE DERIVATIVES

This invention relates to a series of 5-6 fused ring bicyclic heteroaromatic derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

Immune and inflammatory responses involve a variety of cell types with control and co-ordination of the various interactions occurring *via* both cell-cell contacts (e.g integrin interactions with their receptors) and by way of intercellular signalling molecules. A large number of different signalling molecules are involved including cytokines, lymphocytes, chemokines and growth factors.

Cells respond to such intercellular signalling molecules by means of intracellular signalling mechanisms that include protein kinases, phosphatases and phospholipases. There are five classes of protein kinase of which the major ones are the tyrosine kinases and the serine/threonine kinases [Hunter, T., Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T. and Sefton, B.M.; eds. Vol. 200, Academic Press; San Diego, 1991].

One sub-class of serine/threonine kinases is the mitogen activating protein (MAP) kinases of which there are at least three families which differ in the sequence and size of the activation loop [Adams, J. L. *et al*, Progress in Medicinal Chemistry p. 1-60, King, F. D. and Oxford, A. W.; eds. vol 38, Elsevier Science, 2001]: the extracellular regulated kinases (ERKs), the c-Jun NH_2 terminal kinases or stress activated kinases (JNKs or SAP kinases) and the p38 kinases which have a threonine-glycine-tyrosine (TGY) activation motif. Both the JNKs and p38 MAP kinases are primarily activated by stress stimuli including, but not limited to, proinflammatory cytokines e.g.

tumour necrosis factor (TNF) and interleukin-1 (IL-1), ultraviolet light, endotoxin and chemical or osmotic shock.

Four isoforms of p38 have been described (p38α/β/γ/δ). The human p38α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially termed CSAID binding protein-1 (CSBP-1) and CSBP-2 [Lee, J. C. *et al*, Nature (London) 1994, 372, 739-46]. CSBP-2 is now widely referred to as p38α and differs from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons that are conserved in both mouse and human [McDonnell, P. C. et al, Genomics 1995, 29, 301-2]. CSBP-1 and p38α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38β which has 70% identity with p38α. A second form of p38β termed p38β2 is also known and of the two this is believed to be the major form. p38α and p38β2 are expressed in many different tissues. However in monocytes and macrophages p38α is the predominant kinase activity [Lee, J. C., *ibid*; Jing, Y. *et al*, J. Biol. Chem. 1996, 271, 10531-34; Hale, K. K. *et al*, J. Immun. 1999, 162, 4246-52]. p38γ and p38δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have ~63% and ~61% homology to p38α respectively. p38γ is predominantly expressed in skeletal muscle whilst p38δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y. N. *et al* FEBS Lett., 1995, 364,

7095-8012]. This dual phosphorylation is effected by MKK6 and under certain conditions the related enzyme MKK3 (see Figure 1) [Enslen, H. *et al* J. Biol. Chem., 1998, 273, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.

Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF-β-activated kinase) are some of the enzymes identified as upstream activators of for MAPKKs. MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H. Cell, 1998, 95, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor-β (TGF-β). TNF-stimulated activation of p38 is believed to be mediated by the recruitment of TRAF2 [TNF receptor associated factor] and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and others substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1, IL-6, IFN-g and IL-10 is also partially inhibited [Kotlyarov, A. *et al* Nature Cell Biol. 1999, 1, 94-7]. Further, MAPKAP K2 from embryonic stem cells from p38α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. *et al*, J. Exp. Med. 2000, 191, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μM range [Lee, J. C. *et al*, Int. J. Immunopharm. 1988, 10, 835] and exhibit activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J. C. et al, Annals N. Y. Acad. Sci. 1993, 696, 149]. In addition these small molecule inhibitors are known to also decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA2, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P. Trends Cell Biol. 1997, 7, 353-61].

A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and

other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resporption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS related complex.

Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition IL-1 has been linked to diabetes and pancreatic β cells [Dinarello, C. A. J. Clinical Immunology, 1985, 5, 287-97].

IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF and LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis which may contribute to increased adhesion of neutrophils to vascular endothelial cells. Many diseases are characterised by massive neutrophil infiltration. Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysozomal enzyme release and respiratory burst from neutrophils.

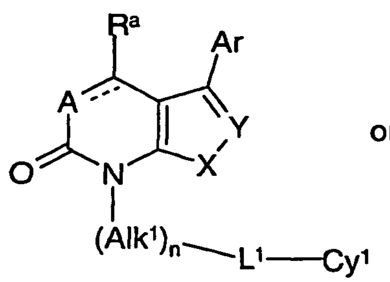
The central role of IL-1 and TNF together with other leukocyte derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin) make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger, *et al*, J. Pharm. Exp. Ther. 1996, 279, 1453-61; Griswold, *et al*, Pharmacol. Comm., 1996, 7, 323-29].

Japanese patent application No. JP09059276 describes a series of pyrazalopyridinones and analogs with utility as herbicides.

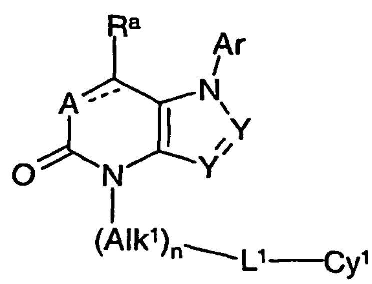
We have now found a group of compounds which are potent and selective inhibitors of p38 kinase (p38α, β, δ and γ) and the isoforms and splice variants thereof, especially p38α, p38β and p38β2. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

Thus according to one aspect of the invention we provide a compound of formula (1a) or (1b):



(1a)

or



(1b)

wherein:

the dashed line represents an optional bond;

A is a -N= atom or a -N(R^b)-, -C(R^b)= or -C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

X is an -O- or -S- atom or -NH- group or substituted N atom;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

for the manufacture of a medicament for the prophylaxis or treatment of a p38 kinase mediated disease or disorder.

This invention also relates to a compound of formula (1a) or (1b) for use in the prophylaxis or treatment of a p38 kinase mediated disease or disorder in a mammal in need thereof.

This invention also relates to a compound of formula (1a) or (1b) for use in the prophylaxis or treatment of a cytokine mediated disease or disorder in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-6 in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof.

This invention more specifically relates to the administration to a mammal of an effective amount of a p38 kinase or cytokine, specifically IL-1, IL-6, IL-8 or TNF, inhibitor of formula (1a) or (1b).

Compounds according to the invention are potent and selective inhibitors of p38 kinases, including all isoforms and splice variants thereof. More specifically the compounds of the invention are inhibitors of p38α, p38β and p38β2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds of formula (1) are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8 include without limitation autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs, host disease or psoriasis.

The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis.

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastic melanoma and multiple myeloma.

Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury.

Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

In addition, p38 inhibitors of this invention also exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2) and are therefore of use in therapy. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly additional p38 mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

Thus TNF mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoiosis, bone resportion disease, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to

infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, viral infections such as HIV, CMV, influenza and herpes; and vetinary viral infections, such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Compounds of the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the TNF inhibiting compounds of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses such as Herpes Zoster and Herpes Simplex.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, diabetes, pancreatic β-cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis, inflammatory bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The increased IL-8 production associated with each of these diseases is responsible for the chemotaxis of neutrophils into

inflammatory sites. This is due to the unique property of IL-8 (in comparison to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in neutrophil infiltration.

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al*, Clin. Infec. Dis., 1997, 26, 840; Grunberg *et al*, Am. J. Crit. Care Med. 1997, 155, 1362; Zhu *et al*, J. Clin. Invest. 1996, 97, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al*, J. Clin. Invest. 1995, 96, 549]. Therefore, p38 inhibitors of the invention may be used for the treatment or prophylaxis of the common cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus or adenovirus infection.

For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine mediated disease the compounds according to the invention may be administered to a human or mammal as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1a) or (1b) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (1a) or (1b) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active

ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1a) or (1b) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds for use according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively the compounds for use according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for

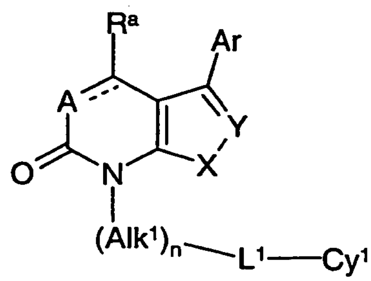
example mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds for use according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH adjusted sterile saline, either with or without a preservative such as bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds for use according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include for example cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

Particular compounds of formula (1a) and formula (1b) form a further aspect of the invention. Thus we provide a compound of formula (1a):



(1a)

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a –N(R^b)-, –C(R^b)= or –C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

X is an –O- or –S- atom or –NH- group or substituted N atom;

Y is a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

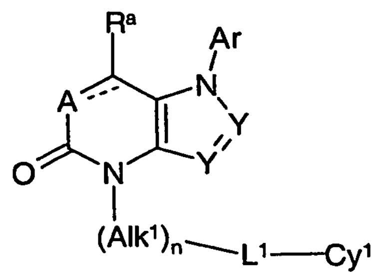
Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

Particular compounds of formula (1a) in which Cy^1 is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group form a further aspect of the invention.

In another particular aspect of the invention and we provide a compound of formula (1b):



(1b)

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a –N(R^b)-, –C(R^b)= or –C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

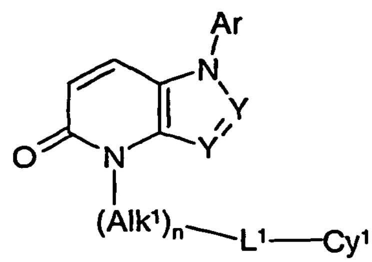
L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

with the proviso that when the compound of formula (1b) is a compound of formula (1c):



(1c)

in which

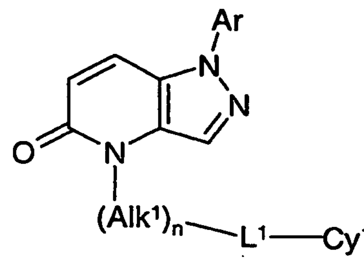
each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH=CH-$, $-CH_2CH=CCl-$, $-CH_2CC-$ or $-CF_2-$ chain then Cy^1 is other than a hydrogen atom; or in which

each Y is a N atom or a CH group, Ar is a 3-chloro-5-trifluoromethylpyridin-2-yl group, L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ chain then Cy^1 is other than a hydrogen atom; or in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a cyclopropyl group; or in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl, 2-chloro-6-fluoro-4-trifluoromethylphenyl or 3-chloro-5-trifluoromethylpyridin-2-yl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a hydrogen atom;

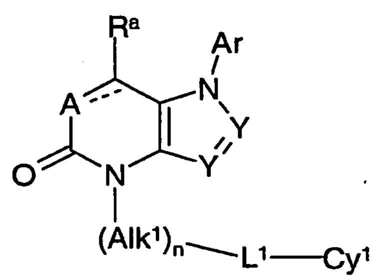
and with the further proviso that when the compound of formula (1b) is a compound of formula (1d):


(1d)

in which:

L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$ chain then Ar is other than a 3-methyl-5-trifluoromethylpyridin-2-yl, 5-trifluoromethylpyridin-2-yl, 3-trifluoromethylpyridin-2-yl, 3,5-difluoropyridin-2-yl, 3,5-dichloropyridin-2-yl or 2-chloro-4-trifluoromethylphenyl group.

Particular compounds of formula (1b) form a further aspect of the invention and we therefore provide a compound of formula and (1b'):


(1b')

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a $-N(R^b)-$, $-C(R^b)=$ or $-C(R^b)(R^c)-$ group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

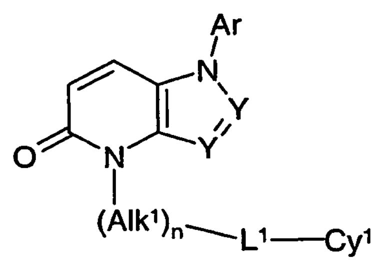
L^1 is a covalent bond or a linker atom or group;

Cy^1 an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

with the proviso that when the compound of formula (1b") is a compound of formula (1c):



(1c)

in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a cyclopropyl group.

It will be appreciated that in the following detailed description of the invention all references to formula (1b) are also references to formulae (1b') unless specifically stated otherwise.

It will be further appreciated that compounds of formulae (1a) and (1b) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formulae (1a) and (1b) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formulae (1a) and (1b) may exist as tautomers, for example keto ($CH_2C{=}O$)-enol ($CH{=}CHOH$) tautomers. Formulae (1a) and (1b) and the

formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

The following general terms as used herein have the stated meaning unless specifically described otherwise.

As used herein the term "alkyl" whether present as a group or part of a group includes straight or branched C_{1-6}alkyl groups, for example C_{1-4}alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl or t-butyl groups. Similarly, the terms "alkenyl" or "alkynyl" are intended to mean straight or branched C_{2-6}alkenyl or C_{2-6}alkynyl groups such as C_{2-4}alkenyl or C_{2-4}alkynyl groups. Optional substituents which may be present on these groups include those optional substituents mentioned hereinafter in relation to Alk^1 when Alk^1 is an optionally substituted aliphatic chain.

The term halogen is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include those alkyl groups just mentioned sustituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CH_2F$ and $-CH_2Cl$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-6}alkoxy e.g. C_{1-4}alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ and $-OCH_2Cl$ groups.

As used herein the term "alkylthio" is intended to include straight or branched C_{1-6}alkylthio, e.g. C_{1-4}alkylthio such as methylthio or ethylthio.

As used herein the term "alkylamino or dialkylamino" is intended to include the groups $-NHR^1$ and $-N(R^1)_2$ [where R^1 is an optionally substituted straight or branched alkyl group]. Where two R^1 groups are present these may be the same or different. In addition where two R^1 groups are present these may be joined together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl group which may contain a further heteroatom or heteroatom containing group such as an –O- or -S- atom or –$N(R^1)$- group. Particular examples of such optionally substituted heterocycloalkyl groups include optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and N'-C_{1-6}alkyl-piperazinyl groups. The optional substituents which may be present on such heterocycloalkyl groups include those optional substituents as described hereinafter in relation to aliphatic chains.

When Alk^1 is present in compounds of formulae (1a) and (1b) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10}aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ chains.

Heteroaliphatic chains represented by Alk^1 in the compounds of formulae (1a) and (1b) include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-L^2CH_2-$, $-CH_2L^2-$, $-L^2CH(CH_3)-$, $-CH(CH_3)L^2-$, $-CH_2L^2CH_2-$, $-L^2CH_2CH_2-$, $-L^2CH_2CH(CH_3)-$, $-CH(CH_3)CH_2L^2-$, $-CH_2CH_2L^2-$, $-CH_2L^2CH_2CH_2-$, $-CH_2L^2CH_2CH_2L^2-$, $-(CH_2)_2L^2CH_2-$, $-(CH_2)_3L^2CH_2-$, $-L^2(CH_2)_2CH_2-$, $-L^2CH_2CHCH-$, $-CHCHCH_2L^2-$ and $-(CH_2)_2L^2CH_2CH_2-$ chains.

When L^2 is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include –O- or -S- atoms or $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-N(R^2)-$ [where R^2 is a hydrogen atom or a straight or branched alkyl group], $-N(R^2)O-$, $-N(R^2)N-$, $-CON(R^2)-$, $-OC(O)N(R^2)-$, $-CSN(R^2)-$, $-N(R^2)CO-$, $-N(R^2)C(O)O-$, $-N(R^2)CS-$, $-S(O)_2N(R^2)-$, $-N(R^2)S(O)_2-$, $-N(R^2)CON(R^2)-$, $-N(R^2)CSN(R^2)-$ or $-N(R^2)SO_2N(R^2)-$ groups. Where L^2 contains two R^2 groups these may be the same or different.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, $-CO_2H$, $-CO_2R^4$ [where R^4 is an optionally substituted straight or branched C_{1-6}alkyl group], e.g. $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, $-CONHR^4$, e.g. $-CONHCH_3$, $-CON(R^4)_2$, e.g. $-CON(CH_3)_2$, $-COR^4$, e.g. $-COCH_3$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol (-SH), $-S(O)R^4$, e.g. –

$S(O)CH_3$, $-S(O)_2R^4$, e.g. $-S(O)_2CH_3$, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino, $-NHR^4$, e.g. $-NHCH_3$ or $-N(R^4)_2$, e.g. $-N(CH_3)_2$ groups. Where two R^4 groups are present in any of the above substituents these may be the same or different.

In addition when two R^4 alkyl groups are present in any of the optional substituents just described these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from –O-, -S-, $-N(R^4)-$, -C(O)- or –C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When L^1 is present in compounds of formulae (1a) and (1b) as a linker atom or group it may be any such atom or group as hereinbefore described in relation to L^2 linker atoms and groups.

Optionally substituted cycloaliphatic groups represented by the group Cy^1 in compounds of the invention include optionally substituted C_{3-10}cycloaliphatic groups. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl or C_{3-10}cycloalkenyl, e.g C_{3-7}cycloalkenyl groups.

Optionally substituted heterocycloaliphatic group represented by the group Cy^1 include optionally substituted C_{3-10}heterocycloaliphatic group. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7}heterocycloalkyl or C_{3-10}heterocycloalkenyl, e.g. C_{3-7}heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom containing groups L^4 in place of or in addition to the ring carbon atoms where L^4 is an atom or group as previously defined for L^2.

Optionally substituted polycycloaliphatic groups represented by the group Cy^1 include optionally substituted C_{7-10}bi-or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group Cy^1 include optionally substituted C_{7-10}bi- or tricycloalkyl or C_{7-10}bi- or tri-cycloalkenyl groups containing one, two, three, four or more L^4 atoms or groups in place of or in addition to the ring carbon atoms.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group Cy^1 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, 5,6-dihydro-2(1H)-pyrazinone, tetrahydropyrimidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, 1,3,5-oxadiazinyl, dihydroisothiazolyl, dihydroisothiazole 1,1-dioxide , e.g. 2,3-dihydroisothiazole 1,1-dioxide, dihydropyrazinyl and tetrahydropyrazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups

represented by the group Cy^1 include one, two, three or more substituents selected from halogen atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, eg. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthiol, e.g. methylthiol or ethylthiol, carbonyl (=O), thiocarbonyl (=S), imino ($=NR^{4a}$) [where R^{4a} is an $-OH$ group or a C_{1-6}alkyl group], or $-(Alk^3)_vR^5$ groups in which Alk^3 is a straight or branched C_{1-3}alkylene chain, v is zero or the integer 1 and R^5 is a C_{3-8}cycloalkyl, $-OH$, $-SH$, $-N(R^6)(R^7)$ [in which R^6 and R^7 is each independently selected from a hydrogen atom or an optionally substituted alkyl or C_{3-8}cycloalkyl group], $-OR^6$, $-SR^6$, $-CN$, $-NO_2$, $-CO_2R^6$, $-SOR^6$, $-SO_2R^6$, $-SO_3R^6$, $-OCO_2R^6$, $-C(O)R^6$, $-OC(O)R^6$, $-C(S)R^6$, $-C(O)N(R^6)(R^7)$, $-OC(O)N(R^6)(R^7)$, $-N(R^6)C(O)R^7$, $-C(S)N(R^6)(R^7)$, $-N(R^6)C(S)R^7$, $-SO_2N(R^6)(R^7)$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)N(R^7)(R^8)$ [where R^8 is as defined for R^6], $-N(R^6)C(S)N(R^7)(R^8)$, $-N(R^6)SO_2N(R^7)(R^8)$ or an optionally substituted aromatic or heteroaromatic group.

Particular examples of Alk^3 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$ chains.

When R^5, R^6, R^7 and/or R^8 is present as a C_{3-8}cycloalkyl groups it may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-6}alkoxy, e.g. methoxy, ethoxy or *i*-propoxy groups.

When the groups R^6 and R^7 or R^7 and R^8 are both alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a

heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from –O-, -S-, –$N(R^7)$-, -C(O)- or –C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When R^5 is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter in relation to Cy^1.

Additionally, when the group Cy^1 is a heterocycloaliphatic or heteropolycycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^5)_p(Alk^4)_qR^9$ in which L^5 is a –C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^6)-$ or $-SO_2N(R^6)-$; p is zero or the integer 1; Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or the integer 1; and R^9 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group as herein described in relation to Cy^1.

When Alk^4 is present as an aliphatic or heteroaliphatic chain it may be for example any aliphatic or heteroaliphatic chain as hereinbefore described for Alk^1.

Optionally substituted aromatic groups represented by the groups Cy^1 include for example monocyclic or bicyclic fused ring C_{6-12}aromatic groups, such as phenyl, 1- or 2-napthyl, 1- or 2-tetrahydronapthyl, indanyl or indenyl groups.

Heteroaromatic groups represented by the groups Cy^1 include for example C_{1-9}heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the

heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, [2,3-dihydro]benzothienyl, benzotriazolyl, indolyl, indolinyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-c]pyrimidinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, imidyl, e.g. succinimidyl, phthalimidyl or naphthalimidyl such as 1,8-naphthalimidyl, pyrazolo[4,3-d]pyrimidinyl, furo[3,2-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyrrolo[3,2-d]pyrimidinyl, pyrazolo[3,2-b]pyridinyl, furo[3,2-b]pyridinyl, thieno[3,2-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, thiazolo[3,2-a]pyyridinyl, pyrido[1,2-a]pyrimidinyl, tetrahydroimidazo[1,2-a]pyrimidinyl and dihydroimidazo[1,2-a]pyrimidinyl groups.

Optional substituents which may be present on aromatic or heteroaromatic groups represented by the group Cy^1 include one, two, three or more

substituents, each selected from an atom or group R^{10} in which R^{10} is R^{10a} or $-L^6Alk^5(R^{10a})_r$, where R^{10a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{11}$ [where R^{11} is an $-L^6Alk^3(R^{10a})_r$, aryl or heteroaryl group], $-CSR^{11}$, $-SO_3H$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-SO_2NH_2$, $-SO_2NHR^{11}$, $-SO_2N(R^{11})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{11}$, $-CSNHR^{11}$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-N(R^{12})SO_2R^{11}$ [where R^{12} is a hydrogen atom or a straight or branched alkyl group], $-N(SO_2R^{11})_2$, $-N(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{11}$, $-N(R^{12})SO_2N(R^{11})_2$, $-N(R^{12})COR^{11}$, $-N(R^{12})CONH_2$, $-N(R^{12})CONHR^{11}$, $-N(R^{12})CON(R^{11})_2$, $-N(R^{12})CSNH_2$, $-N(R^{12})CSNHR^{11}$, $-N(R^{12})CSN(R^{11})_2$, $-N(R^{12})CSR^{11}$, $-N(R^{12})C(O)OR^{11}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other –O- or -S- atoms or $-N(R^{12})-$, -C(O)- or –C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het$ [where -Het is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more other –O- or –S- atoms or $-N(R^{12})-$, -C(O)-, -S(O)- or $-S(O)_2-$ groups], -Het, $-CON(R^{12})Het$, $-CSN(R^{12})Het$, $-N(R^{12})CON(R^{12})Het$, $-N(R^{12})CSN(R^{12})Het$, $-N(R^{12})SO_2N(R^{12})Het$, aryl or heteroaryl groups; L^6 is a covalent bond or a linker atom or group as hereinbefore defined for L^2; Alk^5 is an optionally substituted straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three –O- or -S- atoms or $-S(O)_n-$ [where n is an integer 1 or 2] or $-N(R^{12})-$ e.g. $-N(CH_3)-$ groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

When in the group $-L^6Alk^5(R^{10a})_r$ r is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{10a} may be present on any suitable carbon atom in $-Alk^5$. Where more than one R^{10a} substituent is present these may be

the same or different and may be present on the same or different atom in $-Alk^5$. Clearly, when r is zero and no substituent R^{10a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^5 becomes an alkyl, alkenyl or alkynyl group.

When R^{10a} is a substituted amino group it may be for example a group $-NHR^{11}$ [where R^{11} is as defined above] or a group $-N(R^{11})_2$ wherein each R^{11} group is the same or different.

When R^{10a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{10a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{11}$ or a $-SR^{12}$ group respectively.

Esterified carboxyl groups represented by the group R^{10a} include groups of formula $-CO_2Alk^6$ wherein Alk^6 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^6 group include R^{10a} atoms and groups as described above.

When Alk^5 is present in or as a substituent it may be for example a $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-C(CH_3)_2CH_2-$, $-CH=CH-$, $-CH=CCH_2-$, $-CH_2C=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH_2-$, -CC-, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-CH_2CH_2CC-$ chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{12})-$, e.g. $-N(CH_3)-$ groups. The aliphatic chains represented by Alk^5 may be optionally substituted by one, two or three halogen atoms in addition to any R^{10a} groups that may be present.

Aryl or heteroaryl groups represented by the groups R^{10a} or R^{11} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Cy^1. The aromatic and heteroaromatic groups may be attached to the group Cy^1 in compounds of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

It will be appreciated that when $-NHet^1$ or –Het forms part of a substituent R^{10} the heteroatoms or heteroatom containing groups that may be present within the ring $-NHet^1$ or –Het take the place of carbon atoms within the parent carbocyclic ring.

Thus when $-NHet^1$ or –Het forms part of a substituent R^{10} each may be for example an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-NHet^1$ include those substituents described above when Cy^1 is a heterocycloaliphatic group.

Particularly useful atoms or groups represented by R^{10} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{3-7}cycloalkyl, e.g. cyclobutyl, cyclopentyl, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino, ethylamino, $-CH(CH_3)NH_2$ or $-C(CH_3)_2NH_2$, haloC_{1-6}alkylamino, e.g. fluoroC_{1-6}alkylamino,e.g. $-CH(CF_3)NH_2$ or $-C(CF_3)_2NH_2$, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^6$ [where Alk^6 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylamino-carbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethyl-aminocarbonyl, aminocarbonylamino, C_{1-}

6alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylamino-carbonylamino, e.g. dimethylaminocarbonylamino or diethylamino-carbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylamino-carbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonyl-amino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonyl-amino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkyl-sulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethyl-aminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoyl-amino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethyl-amino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonyl-amino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxy-carbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridyl-methylthio or thiazolylmethylthio groups.

A further particularly useful group of substituents represented by R^{10} when present on aromatic or heteroaromatic groups includes substituents of formula –$L^6Alk^5R^{10a}$ where L^6 is preferably a covalent bond or an –O- or -S- atom or –$N(R^2)$-, -C(O)-, -C(O)O-, -O-C(O)-, -$N(R^2)$CO-, -CON(R^2)- or –$N(R^2)S(O)_2$-

group, Alk^5 is an optionally substituted C_{1-6}alkyl group optionally interrupted by one or two –O- or –S- atoms or –$N(R^{12})$-, -C(O)-, -C(S)-, -$CON(R^{12})$- or –$N(R^{12})$CO- groups and R^{10a} is an optionally substituted Het group as herein defined or an optionally substituted heteroaromatic group as hereinbefore described in relation to Cy^1.

Where desired, two R^{10} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group represented by the group Cy^1.

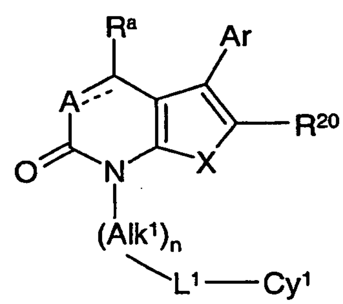
When in compounds of formula (1a) X is a substituted –N- atom or in compounds of formulae (1a) or (1b) Y is a substituted C atom the substituents which may be present on the N or C atom include those R^{10} atoms and groups as hereinbefore defined.

When Ar is present in compounds of formulae (1a) or (1b) as an optionally substituted aromatic or heteroaromatic group it may be any such group as hereinbefore described for Cy^1. Optional substituents which may be present include those R^{10} atoms and groups as described in relation to Cy^1 aromatic and heteroaromatic groups.

One useful group of compounds according to the invention is that where Y is a CH group or a substituted C atom where the substituent on the C atom may in general be any R^{10} atom or group as hereinbefore described or in particular a R^{20} group as hereinafter defined.

A particularly useful group of compounds according to the invention is represented by the compounds of formula (1a).

An especially useful group of compounds according to the invention has the formula (2a):



(2a)

in which

R^{20} is a hydrogen atom or an atom or group R^{10} as hereinbefore defined;

the dashed line, A, R^a, Alk^1, n, L^1, Cy^1, X and Ar are as generally and specifically defined previously;

and the salts, solvates, hydrates and N-oxides thereof.

In general in compounds of formula (1a), (1b) and (2a) R^a is preferably a hydrogen atom or a C_{1-4}alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. Most preferably R^a is a methyl group or most especially a hydrogen atom.

In one particularly preferred class of compounds of formula (1a), (1b) and (2a) the dashed line represents a bond and A is a -C(R^b)= group. In this class of compounds R^b is preferably a C_{1-4}alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. Most preferably R^b is a methyl group or most especially a hydrogen atom.

In one preferred class of compounds of formulae (1a) and (2a) X is a –O- or –S- atom, most preferably a –S- atom.

In another preferred group of compounds of formulae (1a), (1b) and (2a) n is zero.

In another preferred group of compounds of formulae (1a), (1b) and (2a) n is the integer 1 and Alk^1 is preferably an optionally substituted C_{1-6}alkylene chain, especially an optionally substituted –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, –$CH(CH_3)CH_2$- or –$CH_2CH(CH_3)$- chain, most especially a –CH_2- or –CH_2CH_2- chain.

In compounds of formula (2a) and in general in compounds of the invention L^1 is preferably a covalent bond or an –O- or –S- atom or an –N(R^2)-, especially –NH- or –N(CH_3)-, -C(O)-, -C(S)-, -S(O)- or –S(O)$_2$- group. Most preferably L^1 is a covalent bond or an –O- or –S- atom or –NH- group. L^1 is most especially preferably is a covalent bond.

In compounds of formula (2a) and in general in compounds of the invention Cy^1 is preferably an optionally substituted cycloaliphatic, aromatic or heteroaromatic group as hereinbefore generally and particularly defined.

Particularly preferred Cy^1 optionally substituted cycloaliphatic groups include optionally substituted C_{3-7}cycloalkyl groups, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups.

Particularly preferred optional substituents which may be present on Cy^1 optionally substituted cycloaliphatic groups include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl groups, especially C_{1-3}alkyl groups, most especially a methyl group, or a haloC_{1-6}alkyl group, especially a

fluoroC_{1-6}alkyl group, most especially a $-CF_3$ group, or a C_{1-6}alkoxy, especially methoxy, ethoxy, propxy or i-propoxy group, or a haloC_{1-6}alkoxy, especially a fluoroC_{1-6}alkoxy, most especially a $-OCF_3$ group, or a cyano (-CN), esterified carboxyl, especially $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-C(O)R^6$, especially $-C(O)CH_3$, or $-N(R^6)C(O)R^7$, especially $-NHCOCH_3$ group.

Particularly preferred Cy^1 aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

Particularly preferred optional substituents which may be present on Cy^1 aromatic or heteroaromatic groups include atoms or groups $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl groups, especially C_{1-3}alkyl groups, most especially a methyl group, or a haloC_{1-6}alkyl group, especially a fluoroC_{1-6}alkyl group, most especially a $-CF_3$ group, or a C_{1-6}alkoxy, especially methoxy, ethoxy, propxy or i-propoxy group, or a haloC_{1-6}alkoxy, especially a fluoroC_{1-6}alkoxy, most especially a $-OCF_3$ group, or a cyano (-CN), carboxyl ($-CO_2H$), esterified carboxyl ($-CO_2Alk^6$), especially $-CO_2CH_3$, $-CO_2CH_2CH_3$, or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-COR^{11}$, especially $-COCH_3$, or $-N(R^{12})COR^{11}$, especially $-NHCOCH_3$ group.

Further preferred optional substituents which may be present on Cy^1 aromatic or heteroaromatic groups include groups of formula $-L^6Alk^5(R^{10a})_r$ in which r is the integer 1, L^6 is a covalent bond or an –O- or –S- atom or a –$N(R^2)$-, especially –NH- or –$N(CH_3)$-, -C(O)-, -C(S)-, -C(O)O-, -OC(O)-, -$N(R^2)CO$-, especially –NHCO-, or –$CON(R^2)$-, especially –CHNH-group, Alk^5 is a C_{1-6}alkyl chain, especially a –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$- or –$CH_2CH_2CH_2CH_2$- chain and R^{10a} is a substituted hydroxyl group, especially a –OCH_3, -OCH_2CH_3 or –$OCH(CH_3)_2$ group or a substituted amino group, especially a –$N(CH_3)_2$ or –$N(CH_2CH_3)_2$ group or a –Het group, especially an optionally substituted monocyclic C_{5-7}carbocyclic group containing one, two or three –O-, -S-, -$N(R^{12})$-, especially –NH- or –$N(CH_3)$-or –C(O)- groups within the ring structure as previously described, most especially an optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. N-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group or R^{10a} is an optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, such as optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, triazinyl, pyridazinyl, or pyrazinyl group. Particularly preferred optional substituents on the –Het groups just described include hydroxyl (-OH) and carboxyl (-CO_2H) groups or those preferred optional substituents just described in relation to the group Cy^1.

In one preferred class of compounds of formula (2a) R^{20} is an atom or group –R^{10a} or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Preferably R^{20} is a preferred atom or group as just defined for Cy^1. In one particularly preferred class of compounds of formula (2a) R^{20} is a hydrogen atom or a carboxyl (-CO_2H), esterified carboxyl (-CO_2Alk^6), especially -CO_2CH_3, -$CO_2CH_2CH_3$, or -$CO_2C(CH_3)_3$, -CN, -NH_2, -$CONH_2$, -$CONHR^{11}$, -$N(R^{12})SO_2R^{11}$, -$N(R^{12})C(O)OR^{11}$ or –SO_2R^{11} group.

In one particularly preferred group of compounds of formula (1), (1a) and (2a) Cy^1 is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three optional substituents where at least one, and preferably two optional substituents are located *ortho* to the bond joining Cy^1 to the remainder of the compound of formula (1), (1a) or (2a). Particularly preferred *ortho* substituents include halogen atoms, especially fluorine or chlorine atoms, or C_{1-3}alkyl groups, especially methyl groups, C_{1-3}alkoxy groups, especially methoxy, haloC_{1-3}alkyl groups, especially $-CF_3$, haloC_{1-3}alkoxy groups, especially $-OCF_3$, or cyano (-CN), groups. In this class of compounds a second or third optional substituent when present in a position other than the *ortho* positions of the ring Cy^1 may be preferably an atom or group $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as herein generally and particularly described.

Particularly preferred Ar aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

Particularly preferred optional substituents which may be present on Ar aromatic or heteroaromatic groups include atoms or groups $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl groups, especially C_{1-3}alkyl groups, most especially a methyl group, or a haloC_{1-6}alkyl group, especially a fluoroC_{1-6}alkyl group, most especially a $-CF_3$ group, or a C_{1-6}alkoxy, especially methoxy, ethoxy, propxy or i-propoxy

group, or a haloC_{1-6}alkoxy, especially a fluoroC_{1-6}alkoxy, most especially a $-OCF_3$ group, or a cyano (-CN), esterified carboxyl, especially $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-COR^{11}$, especially $-COCH_3$, or $-N(R^{12})COR^{11}$, especially $-NHCOCH_3$ group.

In one particularly preferred class of compounds of formula (2a) the dashed line is present, A is a –CH= group, R^a is a hydrogen atom and X is a –S-atom.

A further particularly useful class of compounds according to the invention has the formula (1b) in which the dashed line is present, A is a –CH= group, R^a, Ar, Alk^1, n and L^1 are as defined for formula (1b), each Y is independently a CH group or substituted C atom and Cy^1 is an optionally substituted aromatic or heteroaromatic group

Particularly useful compounds of the invention include:

Ethyl 6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 7-cyclopropylmethyl-6-oxo-3-phenyl -6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 6-oxo-3-phenyl-7-(3-thienyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(4-fluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(2-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 6-oxo-7-phenyl-3-(4-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(3-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

6-Oxo-3,7-diphenyl-*N*-(2-piperidinoethyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide;

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile;

3,7-Diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one;

Ethyl 3-(2,4-difluorophenyl)-7-[4-(4-methylpiperazin-1-yl)phenyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

1,4-Diphenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one;

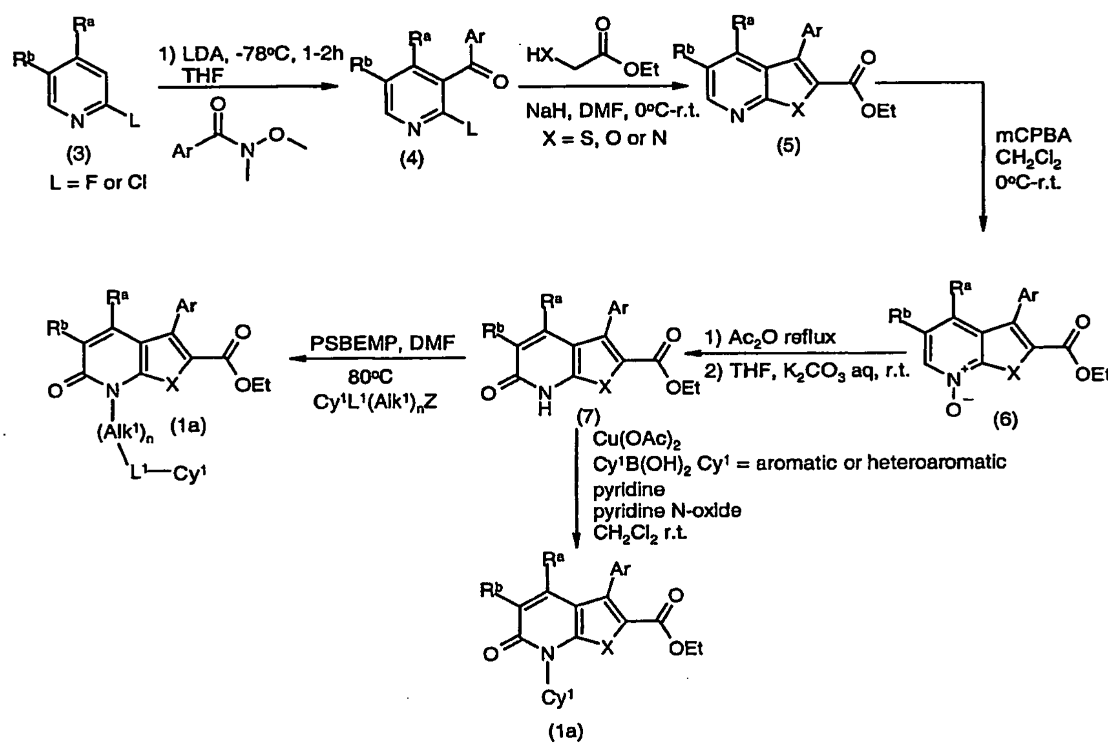
Ethyl 7-(2-chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

and the salts, solvates, hydrates and N-oxides thereof.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, Cy^1, Alk^1, n, L^1, R^a, R^b, R^c, A, X and Y when used in the formulae depicted are to be understood to represent those groups described above in relation to formulae (1a) and (1b) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1a) or (1b) but clearly the description applies equally to the preparation of compounds of formula (2a).

Thus according to a further aspect of the invention a compound of formula (1a) in which Y is a substituted e.g. $-CO_2CH_2CH_3$ substituted C atom may be prepared according to the reactions set out in Scheme 1:

Scheme 1

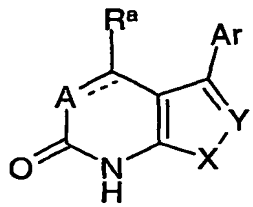


Thus a compound of formula (1a) in which Y is a substituted C atom may be prepared by reaction of a compound of formula (7) with an alkylating agent of formula $Cy^1L^1(Alk^1)_nZ$, where Z is a leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy e.g. phenylsulphonyloxy group.

The reaction may be performed in the presence of a solvent, for example a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an inorganic base such as sodium hydride, or an organic base such as an organic amine, e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene or a resin bound organic amine such as resin bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP), at an elevated temperature, for example 80 to 100ºC.

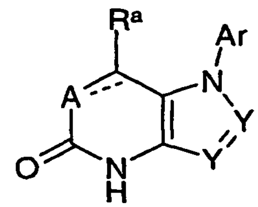
In a further aspect of the invention a compound of formula (1a) in which, for example, L^1 is a covalent bond and n is zero may be prepared by the reaction of a compound of formula (7) with a boronic acid of formula $Cy^1B(OH)_2$. The reaction may be performed in an organic solvent, for example a halogenated hydrocarbon such as dichloromethane or dichloroethane in the presence of a copper reagent, for example a copper (II) reagent such as copper (II) acetate, optionally in the presence of an oxidant, for example 2,2,6,6-tetramethyl-1-piperidinyloxy or pyridine-N-oxide, optionally in the presence of a base, for example an organic amine such as an alkylamine, e.g. triethylamine or an aromatic amine, e.g. pyridine at a temperature from around ambient to the reflux temperature [see for example Chan, D.T. *et al* Tetrahedron Letters, 1998, 2933; Lam, P.Y.S. *et al*, Tetrahedron Letters, 2001, 3415]

Clearly the reactions just described may be used to prepare other compounds of the invention starting from intermediates of formula (7a) or (7b):



(7a)

or



(7b)

for instance compounds of formula (7a) in which Y is a CH group.

Intermediates pyridinones of formula (7) may be prepared from pyridine N-oxides of formula (6) by sequential reaction with an anhydride, for example acetic anhydride at an elevated temperature, for example the reflux temperature followed by reaction with an inorganic base, for example a carbonate such as aqueous potassium carbonate in a solvent such as an ether for example a cyclic ether e.g. tetrahydrofuran at around ambient temperature.

Pyridine N-oxides of formula (6) may be formed from pyridines of formula (5) by standard methods of formation of N-oxides as described hereinafter.

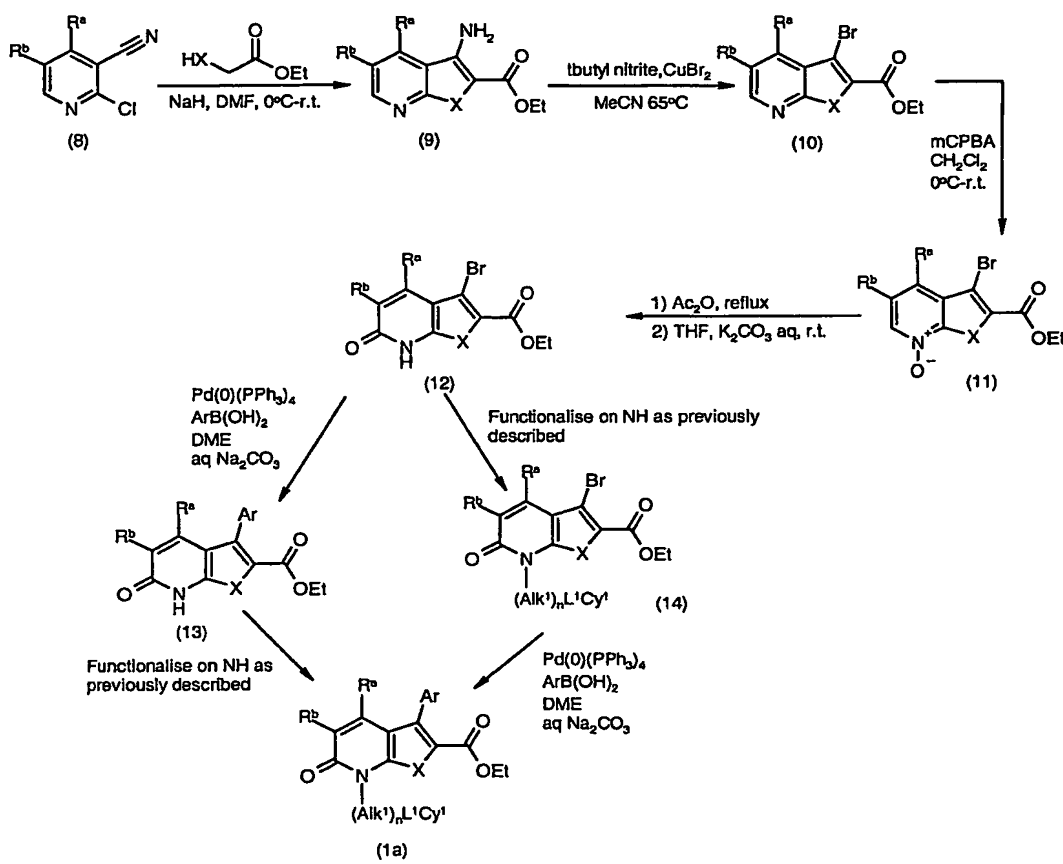
Pyridines of formula (5) may be formed from 2-halopyridyl-(hetero)arylmethanones of formula (4) by reaction with a reagent of formula $HXCH_2CO_2R^{30}$ [where R^{30} is a C_{1-6}alkyl group such as a methyl or ethyl group]. The reaction may be performed in the presence of a solvent such as a substituted amide for example dimethylformamide or an ether e.g. a cyclic ether such as tetrahydrofuran in the presence of a base, for example an inorganic base such as a hydride e.g. sodium hydride or an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene or a trialkylamine such as triethylamine at a temperature between about 0ºC and ambient temperature.

2-Halopyridyl-(hetero)arylmethanones of formula (4) may be prepared from 2-halopyridines of formula (3) by reaction with a base, for example a strong

base such as lithium diisopropylamide or butyl lithium to form a 2-halopyridyl anion and quenching with a (hetero)aryl amide such as a Weinreb amide. The reaction may be performed in the presence of a solvent such as a substituted amide for example dimethylformamide or an ether e.g. a cyclic ether such as, at a temperature of around-78ºC.

According to another aspect of the invention further compounds of formula (1a) may be prepared according to the reactions set out in Scheme 2.

Scheme 2



Thus further compounds of formula (1a) may be prepared from intermediates of formula (13), and intermediates of formula (14) may be prepared from intermediates of formula (12), by functionalisation at the 6-membered ring nitrogen according to the methods as previously described for the conversion of compounds of formula (7) to compounds of formula (1a).

Further compounds of formula (1a) may also be prepared from halogen substituted e.g. bromine substituted intermediates of formula (14), and intermediates of formula (13) may be prepared from halogen substituted e.g. bromine substituted intermediates of formula (12) by reaction with a boronic acid of formula $ArB(OH)_2$. The reaction may be performed in a solvent such as an acyclic ether, for example ethylene glycol dimethyl ether or a cyclic ether, for example tetrahydrofuran or an aromatic hydrocarbon, for example toluene in the presence of an inorganic catalyst such as a palladium catalyst e.g. tetrakis(triphenylphosphine) palladium (0) in the presence of a base, for example an aqueous inorganic base such as aqueous sodium, potassium or caesium carbonate at an elevated temperature, for example around 80ºC.

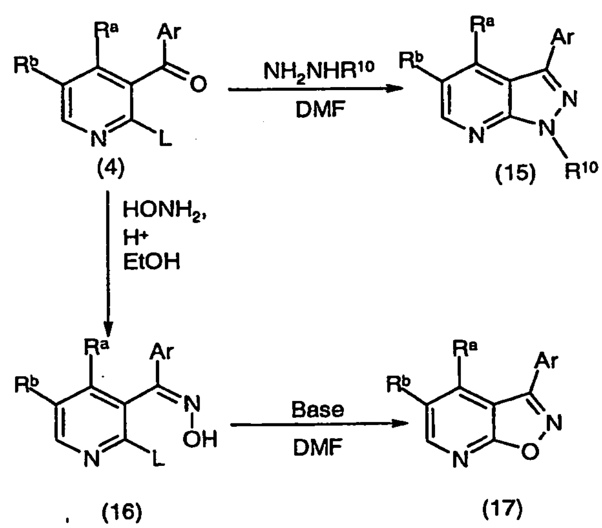
Pyridinones of formula (12) and pyridine N-oxides of formula (11) may be prepared by the methods as hereinbefore described.

Halides, for example bromides, of formula (10) may be prepared by such well known methods as for example the Sandmeyer reaction. Thus for example a bromide of formula (10) may be prepared by treatment of an aryl amine of formula (9) with an alkyl nitrite, for example t-butyl nitrite and a copper salt, for example copper (II) bromide in the presence of a solvent, for example a nitrile such as acetonitrile at a temperature from about 0º to around 65ºC.

Aryl amines of formula (9) may be prepared from halo nitriles of formula (8) by analogous methods to those used to prepare compounds of formula (5) as herein described.

Further 5-6 fused ring bicyclic heteroaromatic intermediates of formulae (15) and (17) may be prepared from intermediates of formula (4) by the methods shown in Scheme 3.

Scheme 3



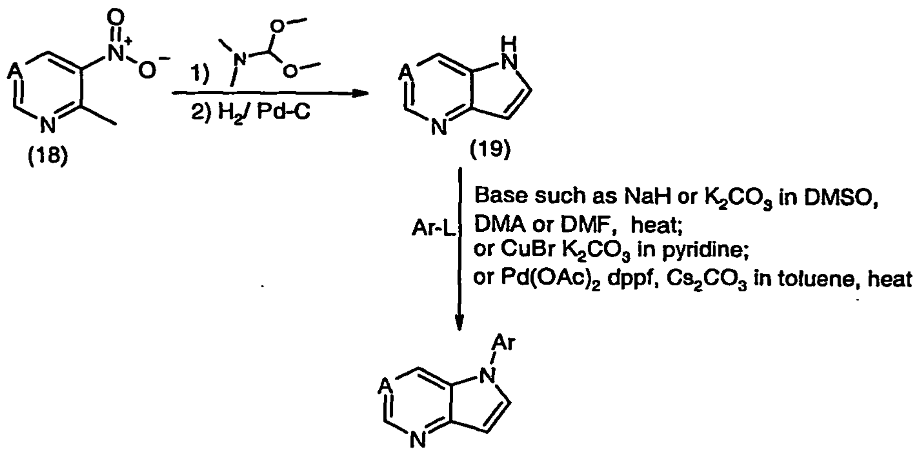
Thus pyrazolo[3,4-b]pyridines of formula (15) may be prepared by reaction of a 2-halopyridyl (or 2-halopyrimidinyl)-(hetero)arylmethanone of formula (4) with an optionally substituted hydrazine of formula $R^{10}NHNH_2$. The reaction may be performed in a solvent such as an amide for example a substituted

amide e.g. dimethylformamide, at an elevated temperature, for example from about 60ºC to the reflux temperature.

Similarly intermediate isoxazolo[3,4-b]pyridines of formula (17) may be prepared by reaction of a 2-halopyridyl (or 2-halopyrimidinyl)-(hetero)arylmethanone of formula (4) with hydroxylamine in the presence of an proton source for example hydrogen chloride in a solvent such as an alcohol, e.g. methanol or ethanol at a temperature from ambient to the reflux temperature to give an intermediate of formula (16) which may be cyclised to an intermediate of formula (17) by reaction with a base, for example an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBU) or an inorganic base such as a hydride e.g. sodium hydride in a solvent such as an amide for example a substituted amide e.g. dimethylformamide or an ether such as a cyclic ether e.g. tetrahydrofuran at a temperature from about 0ºC to ambient temperature.

Further pyrrolo[3,2-b]pyrimidine intermediates of formula (20) may be prepared from intermediates of formula (18) by the methods shown in Scheme 4.

Scheme 4



(18) (19) (20)

Thus a 1H-pyrrolo[3,2-b]pyridine (A=CH) or 1H-pyrrolo[3,2-b]pyrimidine (A=N) of formula (19) may be converted to an intermediate of formula (20) by reaction with a compound of formula Ar-L (in which L is a leaving group such as a halogen atom e.g. a fluorine, chlorine, bromine or iodine atom or a aryl sulfonate such as a triflate). The reaction may be performed in the presence of a base, for example a hydride such as sodium hydride or a carbonate such as potassium or caesium carbonate, in a solvent such as a sulfoxide e.g. dimethyl sulfoxide or an amide e.g. dimethylacetamide or dimethylformamide, at an elevated temperature e.g. from about 60ºC to 120ºC [according to the methods of Glamkowski, E. J. *et al*, J. Med. Chem., 1985, 28, 66 and Stabler, S. R. *et al*, Synth. Commun., 1994, 24, 123-29]. Alternatively the reaction may be performed with a compound of formula Ar-L (in which L is a leaving group such as a halogen atom e.g. a bromine atom or a aryl sulfonate such as a triflate) in the presence of a catalyst such as a copper catalyst e.g. copper (I) bromide in the presence of an inorganic base such as a carbonate e.g. potassium or caesium carbonate in a solvent such as an aromatic amine e.g. pyridine [according to the method of Ishii, H. *et al*, J. Chem. Soc. Perkin Trans. 1, 1989, 2407]. Alternatively the reaction may be performed with a

compound of formula Ar-L (in which L is a leaving group such as a halogen atom e.g. a bromine atom or a aryl sulfonate such as a triflate) in the presence of a catalyst such as a palladium catalyst e.g. palladium (ii) acetate in the presence of an iron catalyst e.g. 1,1'-bis(diphenylphosphino)ferrocene in a solvent such as an aromatic hydrocarbon e.g. toluene at an elevated temperature e.g. between 80ºC and the reflux temperature [according to the method of Mann, G. *et al*, J. Am. Chem. Soc., 1998, 120, 827-8].

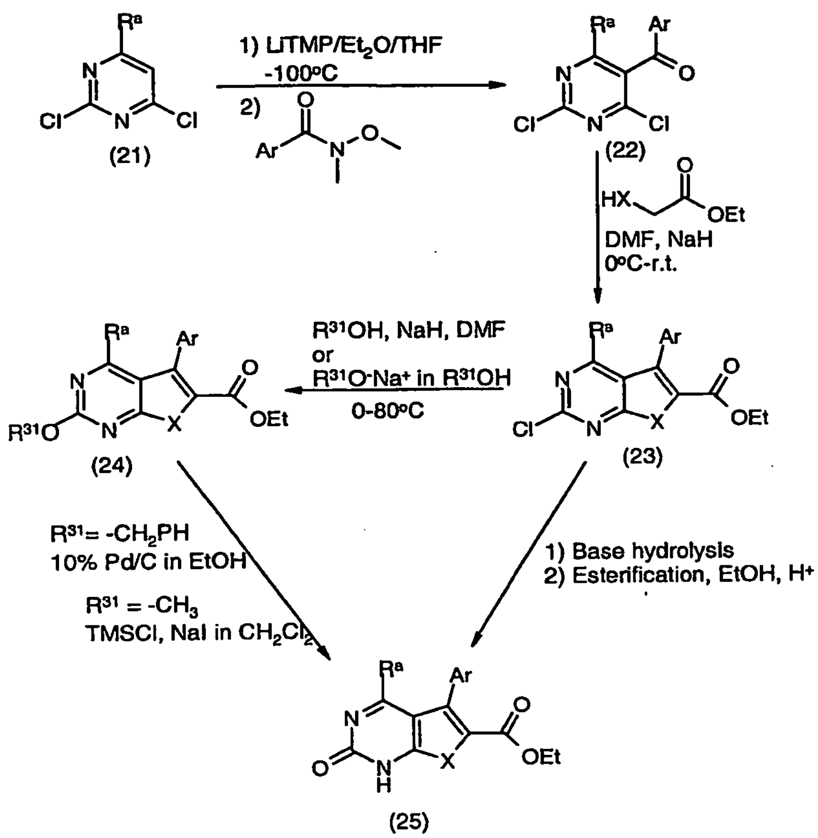
Intermediates of formula (19) may be formed from nitropyridines (A=CH) or nitropyrimidines (A=N) of formula (18) by sequential reaction with a dialkoxymethyl-dimethyl-amine such as dimethoxymethyl-dimethyl-amine followed by catalytic reduction with a palladium catalyst such as palladium on carbon [according to the method of Mahadevan, I. et al, J. Heterocyclic Chem., 1992, 29, 359-67].

Further 5-6 fused ring bicyclic heteroaromatic intermediates for use in the preparation of compounds of formula (1a) and (1b) may be prepared according to the methods of Japanese Patent Application JP9059276.

Such 5-6 fused ring bicyclic heteroaromatic intermediates of formula (15), (17), (19) and (20) as just described may be converted into further compounds of the invention by the particular methods as described above and general methods described below.

Further compounds of the invention in which A is a –N= atom may be prepared according to the methods shown in Scheme 5.

<u>Scheme 5</u>



Thus an intermediate of formula (25) may be converted to a compound of the invention according to the methods as herein described for the conversion of compounds of formula (7) to compounds of formula (1a).

Intermediates of formula (25) may be prepared from intermediates of formula (24) by cleavage of an ether group. Thus when R^{31} is a benzyl group it may be cleaved by such well known methods as catalytic reduction with hydrogen gas in the presence of a catalyst such as a palladium catalyst e.g. palladium on charcoal. When R^{31} is an alkyl ether, e.g. a methyl ether it may be cleaved by reaction with a trialkylsilyl halide such as trimethylsilyl chloride, optionally in the presence of an inorganic halide such as sodium iodide in a solvent such as a halogenated hydrocarbon e.g. dichloromethane or in a nitrile e.g.

acetonitrile [according to the methods of Kundu, N. G. *et al*, J. Chem. Soc. Perkin Trans. I, 1990, 1822].

Intermediates of formula (25) may also be prepared from intermediates of formula (23) sequential by base hydrolysis, for example soudium or potassium hydroxide hydrolysis in a solvent such as an alcohol, e.g. methanol or ethanol at an elevated temperature, e.g. the reflux temperture, followed by re-esterification by reaction with an acidified alcohol, e.g hydrogen chloride saturated ethanol at an elevated temperature, e.g. the reflux temperature.

Intermediates of formula (24) may be prepared from intermediates of formula (23) by reaction with an alkoxide, e.g. sodium methoxide or sodium benzyloxide in a solvent such as an alcohol, e.g. methanol or ethanol at a temperture between about 0ºC and the reflux temperature. Alternatively the reaction may be performed with an alcohol, e.g. methanol or benzyl alcohol in the presence of a strong base, e.g. a hydride such as sodium hydride in an inert solvent such as an amide, e.g. dimethylformamide at a temperature between about 0ºC and 80ºC

Intermediates of formula (23) may be formed from intermediates of formula (22) in a similar manner to that described for the preparation of intermediates of formula (5) form intermediates of formula (4).

Intermediates of formula (22) may be formed from intermediates of formula (21) by reaction with a strong base, e.g. lithium tetramethylpiperidine (LiTMP) in a solvent or mixture of solvents, for example an ether such as diethyl ether of tetrahydrofuran or a mixture thereof at a low temperature, e.g. around -100ºC to form a lithium anion [according to the methods of Queguiner *et al*, J. Het. Chem. 1990, 27, 1377 and Mattson *et al*, J. Org. Chem. 1990, 55, 3410]

which may be further reacted with a Weinreb amide at a temperature from about -78ºC to ambient temperature.

As an alternative a lithium anion as just described may be reacted with an aldehyde of formula ArCHO under the reaction conditions just described to give an intermediate alcohol which may be oxidised give an intermediate of formula (22) by such well known methods as manganese dioxide in a solvent, e.g. a halogenated hydrocarbon such as dichloromethane.

Compounds of the invention and intermediates thereto where A represents a $-N(R^b)-$ or $-C(R^b)(R^c)-$ group may be generated from compounds of the invention or intermediates thereto where A represents a $-N=$ or $-C(R^b)=$ group by reduction, for instance by catalytic hydrogenation using a metal catalyst such as palladium on charcoal in the presence of hydrogen gas at an elevated pressure in a solvent such as an alcohol, e.g. ethanol optionally at an elevated temperaure e.g. between 40 and 60º.

Where in the general processes described above intermediates such as alkylating agents of formula $Cy^1L^1(Alk^1)_nZ$, amides of formula ArC(O)N(OMe)Me, reagents of formula $HXCH_2CO2Et$ and nitroaromatics of formula (18) and any other intermediates required in the synthesis of compounds of the invention are not available commercially or known in the literature, they may be readily obtained from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other intermediates and in particular compounds of formulae (1a) and

(1b) where appropriate functional groups exist in these compounds. Particular examples of such methods are given in the Examples hereinafter.

Thus for example aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile, a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile, an alcohol group may be introduced by using an aldehyde as electrophile and an acid may be introduced by using carbon dioxide as electrophile. Aromatic acids of formula $ArCO_2H$ may also be generated by quenching Grignard reagents of formula ArMgHal with carbon dioxide.

Aromatic acids of formula $ArCO_2H$ generated by this method and acid containing compounds in general may be converted to activated derivatives, e.g. acid halides by reaction with a halogenating agent such as a thionyl halide e.g. thionyl chloride, a phosphorous trihalide such as phosphorous trichloride or a phosphorous pentahalide such as phosphorous pentachloride optionally in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to the reflux temperature, or may be converted into Weinreb amides of formula ArC(O)N(OMe)Me by conversion to the acid halide as just described and subsequent reaction with an amine of formula HN(OMe)Me or a salt thereof, optionally in the presence of a base such as an organic amine, e.g. triethylamine in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to ambient temperature.

Compounds of the invention and intermediates thereto such as compounds of formulae (5), (6), (7), (13) and (14) may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ group (where L^1 is a linker atom or group) may be treated with an alkylating agent Cy^1Z^2 in which Z^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^2H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with the alkylating agents just described but in which Z^2 is replaced by a $-C(O)Z^3$, $C(S)Z^3$, $-N(R^2)COZ^3$or $-N(R^2)C(S)Z^3$ group in which Z^3 is a leaving atom or group as described for Z^2. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which Z^2 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [O-(7-azabenzo-triazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the

presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which Z^2 is replaced by a -S(O)Hal or $-SO_2Hal$ group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^2H$ group as defined above may be coupled with one of the alkylation agents just described but in which Z^2 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

Ester groups such as $-CO_2Alk^6$ and $-CO_2R^4$ in the compound of formula (1) and intermediates thereto may be converted to the corresponding acid [-CO_2H] by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^6 or R^4. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, $-OR^6$ [where R^6 represents an alkyl group such as methyl group] in compounds of formula (1) and intermediates thereto may be

cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{31}$ group (where R^{31} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [e.g. $-CO_2Alk^6$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSR^7$ or $-CSNHR^7$ group may be prepared by treating a corresponding compound containing a $-NHCOR^7$ or $-CONHR^7$ group with a thiation reagent, such as Lawesson's Reagent or P_2S_5, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium triacetoxyborohyride or sodium cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine ($-CH_2NH_2$) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as

carbon, or Raney® nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an alcohol e.g. methanol or ethanol, optionally in the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

In another example, sulphur atoms in the compounds, for example when present in a group L^1 or L^2 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In a further example N-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70ºC to 80ºC, or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent,such as a halogenated hydrocarbon e.g. dichloromethane or an alcohol e.g. tert-butanol at a temperature from the ambient temperature to the reflux temperature.

In another example compounds of formula (12) may be converted to further compounds as formula (13) in which Ar is an optionally substituted aromatic or heteroaromatic group for use in the synthesis of for example compounds of formula (1), using such well know and commonly used palladium mediated reaction conditions as are to be found in the general reference texts *Rodd's Chemistry of Carbon Compounds*, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis,* Volumes 1-19 (John Wiley and Sons, 1999),

Comprehensive Heterocyclic Chemistry, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis*, Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's Comprehensive Organic Transformations* (VCH Publishers Inc., 1989) and *March's Advanced Organic Chemistry* (John Wiley and Sons, 5th Ed., 2001).

Salts of compounds of formula (1a) or (1b) may be prepared by reaction of compounds of formula (1a) or (1b) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1a) or (1b) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1a) or (1b) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1a) or (1b) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in ^{o}C. The following abbreviations are used:

NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
MeOH - methanol;	BOC - butoxycarbonyl;
DCM - dichloromethane;	AcOH - acetic acid;
DIPEA - diisopropylethylamine;	EtOH - ethanol;
Pyr - pyridine;	Ar - aryl;
DMSO - dimethylsulphoxide;	iPr - isopropyl;
Et_2O - diethylether;	Me - methyl;
THF - tetrahydrofuran,	DMF - N,N-dimethylformamide;
MCPBA - 3-chloroperoxybenzoic acid	NBS - N-bromosuccinimide
FMOC - 9-fluorenylmethoxycarbonyl	r.t. – room temperature

DBU - 1,8-Diazabicyclo[5,4-0]undec-7-ene

EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

HOBT - 1-hydroxybenzotriazole hydrate

All NMRs were obtained either at 300MHz or 400MHz.

Compounds were named with the aid of either Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany or ACD Labs Name (v.5.0) supplied by Avanced Chemical Development, Toronto, Canada.

LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following following method: Phenomenex Luna $3\mu C_{18}(2)$ 50x4.6mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of $0.9mLmin^{-1}$, column temperature 40°C.

Gradient:-	Time	%B
	Initial	5
	2.00	95
	3.00	95
	5.0	5
	5.5	end

Intermediate 1

3-Benzoyl-2-fluoropyridine

To a freshly prepared solution of lithium diisopropylamide (22mmol) in dry THF (20mL) under nitrogen and cooled to –78° was added a solution of 2-fluoropyridine (1.94g, 20mmol) in dry THF (10mL). The reaction was stirred for 2.5h at –78° before adding a solution of N-methoxy-N-methyl benzamide (3.47g, 21mmol) in THF (8mL). The reaction mixture was allowed to warm to room temperature over 1.5h and stir at room temperature for 1h. The reaction was quenched with water (50mL), extracted with EtOAc (2x50mL), the extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (5-20% EtOAc in isohexane) to give the title compound as a colourless oil (1.05g, 26%). δH ($CDCl_3$) 8.44 (1H, ddd, J 4.9, 2.0, 1.1Hz), 8.06 (1H, ddd, J 9.3, 7.4, 2.0Hz), 7.84 (2H, dm, J 8.4Hz), 7.66 (1H, tt, J 7.4, 1.3 Hz), 7.52 (2H, tm, J 7.8Hz), 7.38 (1H, ddd, J 6.8, 4.9, 1.9Hz). LCMS (ES^+) RT 3.27 minutes, 202 $(M+H)^+$

Intermediate 2

Ethyl 3-Phenylthieno[2,3-*b*]pyridine-2-carboxylate

To a solution of ethyl 2-mercaptoacetate (0.6mL, 5.5 mmol) in dry DMF (10mL) under nitrogen and cooled with an ice bath was added sodium hydride (220mg of 60% dispersion in oil, 5.75mmol). After hydrogen evolution had ceased the cooling bath was removed and the reaction stirred at room temperature for 30 mins. A solution of Intermediate 1 (920mg, 4.6mmol) in DMF (5mL) was added and the reaction stirred at room temperature for 3h. The reaction was quenched with water (50mL) and extracted with EtOAc (3x50mL). The combined EtOAc layers were washed with brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of the title compound and uncyclised ethyl 2-(3-benzoylpyridin-2-ylsulfanyl)acetate. This crude mixture was dissolved in EtOH (10mL) and sodium ethoxide (10mL of 0.5M solution in EtOH, 5.0mmol) added. The reaction was stirred at room temperature for 45 mins after which time complete conversion of uncyclised material to title compound was observed. The reaction was diluted with EtOAc (50mL), washed with water (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (10%EtOAc in isohexane) to give the title compound as a white solid (780mg, 60%). δH ($CDCl_3$) 8.63 (1H, dd, J 4.5, 1.4Hz), 7.78 (1H, dd, J 8.2, 1.5Hz), 7.41 (3H, m), 7.33-7.32 (2H, m), 7.24 (1H, dd, J 8.2, 4.6Hz), 4.18 (2H, q, J 7.1Hz), 1.15 (3H, t, J 7.1Hz) LCMS (ES^+) RT 3.90 minutes, 284 $(M+H)^+$.

Intermediate 3

Ethyl 3-phenylthieno[2,3-*b*]pyridine-2-carboxylate N-oxide

To a solution of Intermediate 2 in DCM (10mL) was added MCPBA (738mg of 60%w/w, 2.57mmol) and the reaction stirred at r.t. for 6h. The reaction mixture was diluted with DCM (20mL), washed with 2M NaOH (aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (80% EtOAc in isohexane – EtOAc) to give the title

compound as a white solid (670mg, 90%). δH ($CDCl_3$) 8.36 (1H, d, J 6.1 Hz), 7.55-7.49 (4H, m), 7.44-7.39 (2H, m), 7.26 (1H, dd, J 8.2, 6.2 Hz), 4.20 (2H, q, J 7.1 Hz), 1.16 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.18 minutes, 300 $(M+H)^+$

Intermediate 4

Ethyl 6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 3 (400mg, 1.34mmol) and acetic anhydride (20mL) was heated to reflux for 18h. The reaction mixture was concentrated *in vacuo* and the residue co-evapourated with toluene (4x20mL). The crude material was dissolved in THF (20mL) and treated with 10% aqueous K_2CO_3 (20mL). The reaction was stirred at room temperature for 18h and then extracted with EtOAc (3x25mL). The EtOAc extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (40-50% EtOAc in isohexane) to give the title compound as a white solid (193mg, 48%). δH ($CDCl_3$) 7.48 (1H, d, J 9.5Hz), 7.43-7.36 (3H, m), 7.31-7.28 (2H, m), 6.53 (1H, d, J 9.5Hz), 4.13 (2H, q, J 7.1Hz), 1.12 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.25 minutes, 322 ($(M+Na)^+$, 24%), 300 ($(M+H)^+$, 100%).

Intermediate 5

Ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of 2-chloro-3-cyanopyridine (330 g), ethyl 2-mercaptoacetate (361.2 g), sodium carbonate (265 g) and EtOH (1.2L) was heated to reflux for 4.5 hours. It was then cooled to ambient temperature, added to water (10L) and the addition was washed in with water (5L). The resulting slurry was stirred for 30 minutes and then it was filtered. The filter cake was washed with two portions of water (2 x 2.5L) and dried at the pump. The solids were then dried to constant weight under vacuum at 45° to yield the title compound as a brown solid (493.1 g, 93.2%). δH ($CDCl_3$) 8.68 (1H, dd, J 4.7, 1.2 Hz), 7.93 (1H, dd, J 8.5, 1.2 Hz), 7.29 (1H, dd, J 8.5, 4.7 Hz), 5.90 (2H, b), 4.38 (2H, q, J 7.0 Hz), 1.40 (3H, t, J 7.0 Hz). LCMS RT 2.9 minutes, 223 $(M+H)^+$

Intermediate 6

Ethyl 3-bromothieno[2,3-*b*]pyridine-2-carboxylate

Intermediate 5 (363.6g) was added in portions over two hours to a mixture of copper(II) bromide (403.3g), t-butyl nitrite (220.6 g) and acetonitrile (3.6L) stirred at a temperature of 20 to 25°. The mixture was stirred at 20° for 2 hours before it was slowly added to 2M HCl(aq) (4.2L). The reaction mixture slurry was filtered and the solids were washed with water (500 mL). The combined filtrate was extracted with EtOAc (8L), and the EtOAc solution was washed with 2M HCl(aq) (2.2L). The solids were dissolved in EtOAc (6L) and this solution was washed twice with 2M HCl(aq) (4.4L and 2.2L). The two EtOAc solutions were then combined and washed with 2M HCl(aq) (2.2L) and twice with water (2 x 2L). The EtOAc solution was then dried ($MgSO_4$), filtered and concentrated *in vacuo* at 40 mbar and 60° to give a solid residue. This was broken up and dried to constant weight under vacuum at 45° to yield the title compound as a brown solid (458.5g, 97.9%). δH (DMSO-d6) 8.89 (1H, d, J 4.7 Hz), 8.47 (1H, d, J 8.6 Hz), 7.71 (1H, dd, J 8.6, 4.7 Hz), 4.46 (2H, q, J 7.2 Hz), 1.40 (3H, t, J 7.2 Hz). LCMS RT 3.8 minutes, 288 $(M+H)^+$

Intermediate 7

Ethyl 3-Bromothieno[2,3-*b*]pyridine-2-carboxylate N-oxide

To a slurry of Intermediate 6 (214g, 0.747Mol) in DCM (2140mL) under nitrogen was added MCPBA (240g @ 70% = 168g, 0.97Mol) portion wise over 0.5h. The reaction was then stirred at r.t. for 18h. The reaction mixture was quenched with water (800mL) and pH adjusted to 8.5 with 10%w/v sodium carbonate solution (1250mL). The basic aqueous layer was removed and the organic layer washed with water until pH 7. The organic layer was concentrated *in vacuo* and the crude title product was recovered as a tan solid. The crude product was purified by slurrying in methyl *tert*-butyl ether

(600mL) for 1 hr at 0-5° to give the title compound (174g, 77%). δH ($CDCl_3$) 8.44 (1H, dd, J 6.2, 0.8 Hz), 7.87 (1H, dd, J 8.3, 0.8 Hz), 7.48 (1H, dd, J 8.3, 6.2 Hz), 4.49 (2H, q, J 7.1 Hz), 1.48 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.61 minutes, $302(M)^+$

Intermediate 8

Ethyl 3-bromo-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 7 (500mg, 1.66mmol) and DMF (10mL) was set to stir at 0° under nitrogen. To this reaction mixture was added trifluoroacetic anhydride (3.49g, 2.36mL, 16.6mmol) in one portion via syringe. After stirring for 16 hours the volatiles were removed *in vacuo* and the residue co-evaporated with toluene (2x20mL). The crude material was then extracted with EtOAc (2x100mL). The EtOAc extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by a re-slurry in toluene (10mL) to give the title compound as a beige solid (260mg, 52%). δH (DMSO-d6) 12.20 (1H, brs), 7.75 (1H, d, J 9.0Hz), 6.50 (1H, d, J 9.0Hz), 4.15 (2H, q, J 7.1Hz), 1.12 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.86 minutes, 302 ($(M+H)^+$, 100%). MP = 261.7-268.1°C.

Intermediate 9

Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a 2 necked round bottomed flask was added in sequence Intermediate 8 (302mg, 1.00mmol), copper(II) acetate (278mg, 1.50mmol, 150mol%), phenylboronic acid (488mg, 4.00mmol), DCM (5mL) and pyridine (158mg, 2.00mmol). The reaction was stirred at room temperature for 18h with the exclusion of moisture. The reaction was then diluted with DCM (50mL), washed with 2M HCl(aq) (50mL), the aqueous was re-extracted with DCM (50mL). The combined organics were then washed with water (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by a

slurry in methanol (12mL), to give the title compound as a beige solid (270mg, 72%). δH ($CDCl_3$) 7.82 (1H, d, J 8.5Hz), 7.70-7.62 (3H, m), 7.54-7.42 (2H, m), 6.70 (1H, d, J 8.5Hz), 4.15 (2H, q, J 7.1Hz), 1.14 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.75 minutes, 378 $(M+H)^+$. MP = 201.6-206.0°C.

Intermediate 10

Ethyl 3-(4-fluorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 8 (241mg, 0.8mmol), tetrakis(triphenylphosphine)palladium(0) (92mg, 0.08mmol, 10mol%), 2M K_2CO_3 (aq) (0.8mL, 1.6mmol) and 4-fluorophenylboronic acid in ethylene glycol dimethyl ether (10mL) was heated to reflux under nitrogen for 20h. Solvent was removed *in vacuo* and the crude product purified by chromatography on silica (10% THF in DCM) to give the title compound as a white solid (210mg). LCMS (ES^+) RT 3.24 minutes, 318 $(M+H)^+$.

Intermediate 11

6-Oxo-3-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxamide

To a solution of Intermediate 4 (5.13g, 17 mmol) in 1:1 THF water (200mL) was added lithium hydroxide monohydrate (1.6g, 37.4mmol) and the reaction stirred at r.t. overnight. The reaction was incomplete at this time and was therefore concentrated on a rotary evaporator by approx. half and the reaction heated at 60° for 20h. Reaction showed complete conversion to the carboxylic acid at this time. The reaction was diluted with water (50mL) and 2M HCl(aq) added with stirring until a precipitate had formed (pH 1-2). The solid was filtered, washed with several portions of water and dried in a vacuum oven to afford 6-oxo-3-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylic acid as a solid (3.0g). LC RT 2.72 minutes. This compound was suspended in anhydrous DMF (30mL), 1,1'-carbonyldiimidazole (2.14g, 13.2 mmol) added and the reaction stirred for 30 mins. Ammonia (75mL of 25%

aqueous solution) was added and the reaction stirred at r.t. for 1h before being concentrated *in vacuo*. The resultant solid was suspended in 2M HCl(aq), collected by filtration and dried in a vacuum oven to give the title compound as a white solid (2.63g). δH (DMSO-d6) 7.63-7.49 (4H, m), 7.45-7.42 (2H, m), 6.51 (1H, d, J 9.2Hz), 6.28 (1H, bs). LCMS (ES^+) 271 $(M+H)^+$.

Intermediate 12

6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

To a solution of Intermediate 11 (270mg, 1.0mmol) and pyridine (141μL, 1.0mmol) in dry DCM (10mL) was added trifluoroacetic anhydride (160μL, 2.0mmol) and the reaction stirred at r.t. for 16h. Solvent was removed *in vacuo* and the resultant solid suspended in water (30mL) and acidified with 2M HCl(aq) (10mL). The solid was collected by filtration, washed with water (25mL) and dried *in vacuo* to afford the title compound as a white solid (220mg, 87%). δH (DMSO-d6) 7.85 (1H, d, J 9.1Hz), 7.63-7.58 (5H, m), 6.69 (1H, d, J 9.1Hz). LCMS (ES^+) 253 $(M+H)^+$.

Intermediate 13

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-sulfonyl chloride

To a solution of the compound of Example 84 (675mg, 2.5mmol) in dry DCM (20mL) cooled to –78° was added chlorosulfonic acid (1.72g, 14.7mmol) over 5 mins. After 15 minutes reaction was removed from the cooling bath and stirred at r.t. for 1h. Reaction was poured onto ice-water and extracted with DCM. The combined DCM extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow solid (65mg).

Intermediate 14

Ethyl 3-(2,4-difluorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

The title compound was prepared from Intermediate 8 and 2,4-difluorophenylboronic acid following the analogous procedure described for Intermediate 10. This gave the title compound as a white solid LCMS (ES^+) 336 $(M+H)^+$.

Intermediate 15

1-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine

1*H*-Pyrrolo[3,2-*b*]pyridine (0.5g, 4.24mmol), phenylboronic acid (1.03g, 8.44mmol), copper(II) acetate (1.54g, 8.48mmol), and 4A molecular sieves (2g), were suspended in DCM (10mL). Triethylamine (1.19mL, 8.5mmol) and pyridine (0.7mL, 8.65mmol) were added and the reaction stirred at r.t. for three days. The reaction mixture was diluted with further DCM, filtered and concentrated *in vacuo*. Chromatography (silica, EtOAc) gave the title compound (325mg). δH ($CDCl_3$) 7.80 (1H, d, J 8.2Hz), 7.54-7.30 (7H, m), 7.15 (1H, brs), 6.88 (1H, brs). LCMS (ES^+) RT 1.20 minutes, 195 $(M+H)^+$.

Intermediate 16

1-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine 4-oxide

Intermediate 15 (307mg, 1.58mmol) was dissolved in DCM (5mL) and treated with MCPBA (356mg, 2.06mmol). After stirring for eighteen hours at r.t. the reaction was diluted with DCM, washed twice with 2M sodium hydroxide, dried (sodium sulphate) and concentrated *in vacuo* to give the title compound (285mg). δH ($CDCl_3$) 8.15 (1H, d, J 6.2Hz), 7.55-7.47 (2H, m), 7.42-7.37 (5H, m), 7.07, (1H, dd, J 0.7, 3.5Hz), 7.01 (1H, dd, J 6.2, 8.4Hz). LCMS (ES^+) RT 2.527 minutes, 211 $(M+H)^+$.

Intermediate 17

1-Phenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one

Intermediate 16 (273mg, 1.3mmol) was dissolved in DMF (3mL) and treated at 0° with trifluoroacetic anhydride (1.8mL, 13mmol), was allowed to warm to r.t. and stir for two hours. The reaction was diluted with toluene and

concentrated *in vacuo*, re-dissolved in EtOH and concentrated again to give the title compound as an olive coloured solid (420mg). δH ($CDCl_3$) 8.10 (1H, d, J 9.2Hz), 7.72-7.51 (6H, m), 6.85-6.82 (2H, m). LCMS (ES^+) RT 2.668 minutes 211$(M+H)^+$.

Example 1

Ethyl 6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To an oven dried flask was added in sequence 4Å molecular sieves (33mg), phenylboronic acid (82mg, 0.67mmol), DCM (3mL), pyridine (53mg, 0.67mmol), Intermediate 4 (100mg, 0.33mmol), copper(II) acetate (6mg, 0.033mmol, 10mol%) and pyridine N-oxide (34mg, 0.36mmol). The reaction was stirred at room temperature for 18h with the exclusion of moisture. The reaction was then diluted with DCM (20mL), washed with 2M HCl(aq) (2x10mL), 2M NaOH(aq) (3x10mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (DCM – 1% MeOH in DCM) to give the title compound as a buff solid (95mg, 77%). δH ($CDCl_3$) 7.68-7.56 (3H, m), 7.54-7.42 (6H, m), 7.40-7.38 (2H, m), 6.70 (1H, d, J 9.6Hz), 4.15 (2H, q, J 7.1Hz), 1.14 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.87 minutes, 376 $(M+H)^+$.

Example 2

Ethyl 7-cyclopropylmethyl-6-oxo-3-phenyl -6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a solution of Intermediate 4 (90mg, 0.3mmol) in dry DMF (3mL) was added polystyrene supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP, 177mg) and cyclopropylmethyl bromide (101mg, 73µL, 0.75mmol). The reaction was then heated to 80° under nitrogen for 18h. The crude reaction mixture was filtered to remove PS-BEMP and the resin washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by chromatography (DCM – 1% MeOH in

DCM) to give the title compound as a brown gum (57mg, 54%). Recrystallisation from diisopropyl ether gave the title compound as brown needles (30mg). δH ($CDCl_3$) 7.44-7.35 (3H, m), 7.31-7.24 (4H, m), 6.45 (1H, d, J 9.5Hz), 4.14 (2H, q, J 7.1Hz), 4.04 (2H, d, J 7.1Hz), 1.42 (1H, m), 1.12 (3H, t, J 7.1Hz), 0.53 (4H, m). LCMS (ES^+) RT 4.04 minutes, 354 $(M+H)^+$.

Example 3

Ethyl 7-(4-dimethylaminophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To an oven dried flask was added in sequence 4-dimethylaminophenylboronic acid (551mg, 3.34mmol), DCM (10mL), pyridine (0.27mL, 3.34mmol), Intermediate 4 (500mg, 1.67mmol), copper(II) acetate (34mg, 0.17mmol, 10mol%) and pyridine N-oxide (318mg, 3.34mmol). The reaction was stirred at r.t. for 24h with the exclusion of moisture. The reaction was then diluted with DCM (20mL), washed with saturated NH_4Cl(aq), $NaHCO_3$ (aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (5-10% EtOAc in DCM) to give the title compound as a white solid (150mg, 21%). δH (DMSO-d6) 7.51-7.49 (3H, m), 7.42-7.40 (3H, m), 7.30 (2H, d, J 9.0Hz), 6.89 (2H, d, J 9.0Hz), 6.53 (1H, d, J 9.6Hz), 4.07 (2H, q, J 7.1Hz), 3.31 (6H, s), 1.06 (3H, t, J 7.1Hz). LCMS (ES^+) RT 4.10 minutes, 419 $(M+H)^+$.

General procedure for the preparation of Ethyl 7-aryl-6-oxo-3-phenyl-6,7-tetrahydrothieno[2,3-b]pyridine-2-carboxylates

The compounds of the following Examples 4-16 were prepared by parallel synthesis using a Radleys Carousel reaction station (Radleys Ltd., Saffron Walden, U.K.) following a procedure similar to that described for Example 3. Therefore to each oven dried reaction tube in the Carousel was added a magnetic stirrer, the appropriate arylboronic acid (1.0mmol), DCM (5mL), pyridine (0.08mL, 1.0mmol), Intermediate 4 (150mg, 0.5mmol), copper(II)

acetate (10mg, 0.05mmol, 10mol%) and pyridine N-oxide (95mg, 1.0mmol). The reactions were stirred at r.t. for 18h with the exclusion of moisture. Each reaction was then diluted with DCM (20mL), washed with saturated NH_4Cl(aq), $NaHCO_3$(aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified on silica eluting with 0-25% EtOAc in DCM to give the title compounds as solids.

Example 4

Ethyl 7-(4-methoxyphenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH (DMSO-d6) 7.51-7.39 (8H, m), 7.19 (2H, d, J 9.0Hz), 6.55 (1H, d, J 9.6Hz), 4.08 (2H, q, J 7.1Hz), 3.88 (3H, s), 1.05 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.85 minutes, 406 $(M+H)^+$.

Example 5

Ethyl 7-(3-methoxyphenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH (DMSO-d6) 7.59 (1H, t, J 8.3Hz), 7.51 (3H, m), 7.49 (1H, m), 7.46 (2H, m), 7.18 (2H, m), 7.11 (1H, m), 6.57 (1H, d, J 9.7Hz), 4.06 (2H, q, J 7Hz), 3.82 (3H, s), 1.07 (3H, t, J 7Hz). LCMS (ES^+) RT 3.87 minutes, 406 $(M+H)^+$.

Example 6

Ethyl 6-oxo-3-phenyl-7-(4-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH (DMSO-d6) 7.53-7.40 (10H, m), 6.55 (1H, d, J 9.7Hz), 4.07 (2H, q, J 7.1Hz), 2.45 (3H, s), 1.06 (3H, t, J 7.1Hz). LCMS (ES^+) RT 4.11 minutes, 390 $(M+H)^+$.

Example 7

Ethyl 7-(5-Indolyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH (DMSO-d6) 11.48 (1H, bs), 7.71 (1H, s), 7.64 (1H, d, J 8.6Hz), 7.55-7.16 (7H, m), 7.13 (1H, d, J 2.1Hz), 6.58 (1H, m), 6.57 (1H, d, J 9.6Hz), 4.05 (2H, q, J 7.1Hz), 1.03 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.73 minutes, 415 $(M+H)^+$.

Example 8

Ethyl 6-oxo-3-phenyl-7-(3-thienyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH (DMSO-d6) 8.04 (1H, dd, *J* 3.1, 1.4Hz), 7.85 (1H, dd, *J* 5.1, 3.1Hz), 7.41 (3H, m), 7.39 (3H, m), 7.28 (1H, d, *J* 1.4Hz), 6.55 (1H, d, *J* 9.7Hz), 4.09 (2H, q, *J* 7.1Hz), 1.06 (3H, t, *J* 7.1Hz). LCMS (ES^+) RT 3.83 minutes, 382 $(M+H)^+$.

Example 9

Ethyl 6-oxo-3-phenyl-7-(4-trifluoromethoxyphenyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.20 minutes 460 $(M+H)^+$.

Example 10

Ethyl 7-(3-fluorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.91 minutes 394 $(M+H)^+$.

Example 11

Ethyl 7-(4-fluorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.88 minutes 394 $(M+H)^+$.

Example 12

Ethyl 7-(4-chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.14 minutes 410 $(M+H)^+$.

Example 13

<u>Ethyl 7-(3-cyanophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate</u>

LCMS (ES^+) RT 3.72 minutes 401 $(M+H)^+$.

<u>Example 14</u>

<u>Ethyl 6-oxo-3-phenyl-7-(3-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate</u>

LCMS (ES^+) RT 4.09 minutes, 390 $(M+H)^+$.

<u>Example 15</u>

<u>Ethyl 6-oxo-3-phenyl-7-(4-trifluoromethylphenyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate</u>

LCMS (ES^+) RT 4.22 minutes, 444 $(M+H)^+$.

<u>Example 16</u>

<u>Ethyl 7-(3-bromophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate</u>

LCMS (ES^+) RT 4.24 minutes, 454 $(M+H)^+$.

<u>Example 17</u>

<u>Ethyl 3-(4-fluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate</u>

To an oven dried flask was added in sequence phenylboronic acid (78mg, 0.64mmol), DCM (5mL), pyridine (0.64mmol), Intermediate 10 (100mg, 0.32mmol), copper(II) acetate (0.032mmol, 10mol%) and pyridine N-oxide (0.35mmol). The reaction was stirred at r.t. for 48h with the exclusion of moisture. The reaction was then diluted with DCM (20mL), washed with saturated NH_4Cl(aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-5% THF in DCM) to give the <u>title compound</u> as a white solid (75mg). δH ($CDCl_3$) 7.70-7.56 (3H, m),

7.50-7.42 (3H, m), 7.40-7.32 (2H, m), 7.25-7.15 (2H, m), 6.64 (1H, d, J 9.6Hz), 4.16 (2H, q, J 7Hz), 1.17 (3H, t, J 7Hz). LCMS (ES$^+$) RT 3.77 minutes, 394 $(M+H)^+$. $C_{22}H_{16}NFO_3S$ requires C 67.16%, H 4.10%, N 3.56%; found C 67.16%, H 4.10%, N 3.54%.

Example 18

Ethyl 7-(3-chlorophenyl)-3-(4-fluorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To an oven dried flask was added in sequence 3-chlorophenylboronic acid (108mg, 0.688mmol), dichloroethane (5mL), pyridine (0.056mL, 0.688mmol), Intermediate 10 (109mg, 0.344mmol), copper(II) acetate (8mg, 0.034mmol, 10mol%) and pyridine N-oxide (36mg, 0.38mmol). The reaction was heated at 70° for 48h with the exclusion of moisture. The reaction was then diluted with DCM (20mL), washed with saturated NH_4Cl(aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-5% THF in DCM) to give the title compound as a white solid (75mg). LCMS (ES$^+$) RT 3.93 minutes, 428 $(M+H)^+$.

Example 19

Ethyl 6-oxo-7-phenyl-3-(2-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

2M K_2CO_3(aq) (0.25mL, 0.5mmol) was added to a solution of Intermediate 9 (100mg, 0.266mmol), Tetrakis(triphenylphosphine)palladium(0) (30mg, 0.027mmol, 10mol%) and 2-tolylboronic acid (44mg, 0.32mmol) in ethylene glycol dimethyl ether (4mL) and the reaction heated to reflux for 24h under nitrogen. The mixture was diluted with water (10mL), extracted with DCM (2x8mL), the combined DCM extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-20% EtOAc in DCM) to give the title compound as a white solid (57mg). δH ($CDCl_3$) 7.60-7.48 (3H, m), 7.40 (2H, m), 7.27-7.10 (4H, m), 7.07 (1H, m),

6.51 (1H, d, J 9Hz), 4.03 (2H, q, J 7Hz), 2.06 (3H, s), 0.99 (3H, t, J 7Hz). LCMS (ES$^+$) RT 3.87 minutes, 390 (M+H)$^+$. $C_{23}H_{19}NO_3S$ requires C 70.93%, H 4.92%, N 3.60%; found C 70.66%, H 4.95%, N 3.52%.

General procedure for the preparation of Ethyl 3-aryl-6-oxo-7-phenyl-6,7-tetrahydrothieno[2,3-b]pyridine-2-carboxylates

The compounds of the following Examples 20-43 were prepared by parallel synthesis using a Radleys Carousel reaction station (Radleys Ltd., Saffron Walden, U.K.) following a procedure similar to that described for the compound of Example 19. Each reaction tube in the Carousel was charged with the appropriate arylboronic acid (0.32mmol, 1.2equiv.), Intermediate 9 (100mg, 0.266mmol), tetrakis(triphenylphosphine)palladium(0) (30mg, 10mol%) and a magnetic stirrer bar. Ethylene glycol dimethyl ether (4mL) was added to each tube followed by 2M K_2CO_3(aq) (0.25mL, 5mmol) and the reactions heated to reflux under nitrogen for 24h. Each reaction was then diluted with water (10mL), extracted with DCM (2x8mL) and the combined DCM extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified on silica eluting with 0-25% EtOAc in DCM to give the title compounds as solids.

Example 20

Ethyl 6-oxo-7-phenyl-3-(3-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH (DMSO-d6) 7.70-7.60 (3H, m), 7.56 (2H, m), 7.45 (1H, d, J 10Hz), 7.37 (1H, d, J 7Hz), 7.36 (1H, m), 7.27 (2H, m), 6.55 (1H, d, J 10Hz), 4.03 (2H, q, J 7Hz), 2.38 (3H, s), 1.05 (3H, t, J 7Hz). LCMS (ES$^+$) RT 3.93 minutes, 390 (M+H)$^+$. $C_{23}H_{19}NO_3S$ requires C 70.93%, H 4.92%, N 3.60%; found C 70.74%, H 4.95%, N 3.60%.

Example 21

Ethyl 6-oxo-7-phenyl-3-(4-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.70-7.50 (3H, m), 7.48-7.30 (3H, m), 7.25-7.15 (4H, m), 6.52 (1H, d, J 10Hz), 4.07 (2H, q, J 7Hz), 2.36 (3H, s), 1.08 (3H, t, J 7Hz). LCMS (ES^+) RT 3.94 minutes, 390 $(M+H)^+$. $C_{23}H_{19}NO_3S$ requires C 70.93%, H 4.92%, N 3.60%; found C 70.42%, H 4.92%, N 3.58%.

Example 22

Ethyl 3-(2-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.60-7.50 (3H, m), 7.48-7.30 (3H, m), 7.27 (1H, d, J 10Hz), 7.16 (1H, m), 7.01-6.94 (2H, m), 6.51 (1H, d, J 10Hz), 4.05 (2H, q, J 7Hz), 3.71 (3H, s), 1.03 (3H, t, J 7Hz). LCMS (ES^+) RT 3.67 minutes, 406 $(M+H)^+$. $C_{23}H_{19}NO_4S$ requires C 68.13%, H 4.72%, N 3.45%; found C 67.87%, H 4.71%, N 3.37%.

Example 23

Ethyl 3-(2-fluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.80-7.50 (3H, m), 7.49-7.25 (3H, m), 7.48-7.10 (4H, m), 6.55 (1H, d, J 10Hz), 4.07 (2H, q, J 7Hz), 1.06 (3H, t, J 7Hz). LCMS (ES^+) RT 3.71 minutes, 394 $(M+H)^+$. $C_{22}H_{16}NFO_3S$ requires C 67.16%, H 4.10%, N 3.56%; found C 66.99%, H 4.05%, N 3.49%.

Example 24

Ethyl 3-(3-chlorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.68-7.58 (3H, m), 7.48-7.32 (5H, m), 7.28 (2H, m), 6.66 (1H, d, J 10Hz), 4.17 (2H, q, J 7Hz), 1.16 (3H, t, J 7Hz). LCMS (ES^+) RT 3.96 minutes,

410 $(M+H)^+$. $C_{22}H_{16}NClO_3S$ requires C 64.47%, H 3.93%, N 3.42%; found C 64.47%, H 3.94%, N 3.35%.

Example 25

Ethyl 3-(2-chlorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.60-7.05 (10H, m), 6.53 (1H, d, J 10Hz), 4.04 (2H, q, J 7Hz), 1.01 (3H, t, J 7Hz). LCMS (ES^+) RT 3.87 minutes, 410 $(M+H)^+$. $C_{22}H_{16}NClO_3S$ requires C 64.47%, H 3.93%, N 3.42%; found C 64.19%, H 3.97%, N 3.41%.

Example 26

Ethyl 3-(5-chloro-2-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.60-7.45 (3H, m), 7.43-7.34 (2H, m), 7.32 (1H, dd, J 9, 3Hz), 7.26 (1H, d, J 10Hz), 7.14 (1H, d, J 3Hz), 6.88 (1H, d, J 8Hz), 6.53 (1H, d, J 10Hz), 4.08 (2H, m), 3.69 (3H, s), 1.06 (3H, t J 7Hz). LCMS (ES^+) RT 4.27 minutes, 440 $(M+H)^+$.

Example 27

Ethyl 3-(4-fluoro-2-methylphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.60-7.48 (3H, m), 7.45-7.37 (2H, m), 7.18 (1H, m), 7.04 (1H, dd, J 8, 6Hz), 6.98-6.89 (2H, m), 6.52 (1H, d, J 9Hz), 4.04 (2H, q, J 7Hz), 2.06 (3H, s), 1.03 (3H, t, J 7Hz). LCMS (ES^+) RT 4.28 minutes, 408 $(M+H)^+$.

Example 28

Ethyl 3-(2,3-dichlorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.60-7.53 (2H, m), 7.51-7.46 (2H, m), 7.45-7.30 (2H, m), 7.25 (1H, t, J 7.5Hz), 7.19 (1H, d, J 10Hz), 7.13 (1H, dd, J 7.5, 1.5Hz), 6.54 (1H, d, J 10Hz), 4.04 (2H, m), 1.02 (3H, t, J 7Hz). LCMS (ES^+) RT 4.49 minutes, 444 $(M+H)^+$.

Example 29

Ethyl 3-(2,4-difluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.60-7.47 (3H, m), 7.42-7.33 (2H, m), 7.31 (1H, dd, *J* 10, 1Hz), 7.23 (1H, q with F coupling, *J* 8Hz), 6.98-6.85 (2H, m), 6.56 (1H, d, *J* 10Hz), 4.12 (2H, m), 1.08 (3H, t *J* 7Hz). LCMS (ES^+) RT 4.09 minutes, 412 $(M+H)^+$.

Example 30

Ethyl 3-(3-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.74 minutes, 406 $(M+H)^+$.

Example 31

Ethyl 3-(4-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.72 minutes, 406 $(M+H)^+$. $C_{23}H_{19}NO_4S$ requires C 68.13%, H 4.72%, N 3.45%; found C 67.96%, H 4.70%, N 3.40%.

Example 32

Ethyl 3-(3-cyanophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.57 minutes, 401 $(M+H)^+$.

Example 33

Ethyl 3-(4-cyanophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.58 minutes, 401 $(M+H)^+$.

Example 34

Ethyl 3-(3-fluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.78 minutes, 394 $(M+H)^+$. $C_{22}H_{16}NFO_3S$ requires C 67.16%, H 4.10%, N 3.56%; found C 67.06%, H 4.10%, N 3.54%.

Example 35

Ethyl 3-(4-chlorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.05 minutes, 410 $(M+H)^+$. $C_{22}H_{16}NClO_3S$ requires C 64.47%, H 3.93%, N 3.42%; found C 64.31%, H 3.93%, N 3.45%.

Example 36

Ethyl 3-(2,4-dichlorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.70 minutes, 445 $(M+H)^+$.

Example 37

Ethyl 3-(2,5-dichlorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.57 minutes, 445 $(M+H)^+$.

Example 38

Ethyl 3-(5-fluoro-2-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.98 minutes, 424 $(M+H)^+$.

Example 39

Ethyl 3-(2,6-dimethylphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.04 minutes, 404 $(M+H)^+$.

Example 40

Ethyl 6-oxo-7-phenyl-3-(3-pyridyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.00 minutes, 377 $(M+H)^+$.

Example 41

Ethyl 6-oxo-7-phenyl-3-(2-trifluoromethylphenyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.80 minutes, 444 $(M+H)^+$.

Example 42

Ethyl 6-oxo-7-phenyl-3-(3-trifluoromethylphenyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.97 minutes, 444 $(M+H)^+$.

Example 43

Ethyl 6-oxo-7-phenyl-3-(4-trifluoromethylphenyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.99 minutes, 444 $(M+H)^+$.

Example 44

Ethyl 6-oxo-3-phenyl-7-(3-pyridinyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 4 (299mg, 1.0mmol), pyridine-3-boronic acid (246mg, 2.0mmol), pyridine-*N*-oxide (115mg, 1.2mmol), copper(II) acetate (182mg, 1.0mmol) and pyridine (0.160mL, 2.0mmol) in DCM (20mL) was

stirred at r.t. for 3 days. The mixture was diluted with DCM (30mL) and washed with saturated NH_4Cl(aq) plus ammonia (pH 10, 2 x 100mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (3% MeOH in DCM) to give the title compound as a white solid (35mg, 9%). δH ($CDCl_3$) 9.00 (1H, d, J 4.5Hz), 8.95 (1H, s), 8.01 (1H, ddd, J 1.5, 2.4, 8.1Hz), 7.76 (1H, dd, J 4.7, 8.1Hz), 7.68-7.52 (4H, m), 7.55-7.52 (2H, m), 6.77 (1H, d, J 9.7Hz), 4.31 (2H, q, J 7.1Hz), 1.30 (3H, t, J 7.1Hz). *m/z* (ES^+) 377.0 $(M+H)^+$.

Example 45

Ethyl 7-benzyl-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Sodium hydride (32mg of 60% w/w suspension in oil, 0.8mmol, 1.2equiv.) was added to a solution of Intermediate 4 (200mg, 0.67mmol) in anhydrous DMF (5mL) under nitrogen and cooled with an ice bath. The reaction was stirred for 5 minutes before adding benzyl bromide (0.12mL, 1.0mmol, 1.5 equiv.). The reaction was heated at 60° for 18h. The reaction was partitioned between water and EtOAc, the EtOAc extracts were dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was purified by chromatography on silica (0-20% EtOAc in DCM) to give the title compound as an off-white solid (80mg). δH ($CDCl_3$) 7.60-7.20 (11H, m), 6.51 (1H, d, J 10Hz), 5.33 (2H, s), 4.08 (2H, q, J 7Hz), 1.07 (3H, t, J 7Hz). LCMS (ES^+) RT 4.05 minutes, 390 $(M+H)^+$.

General procedure for the preparation of Ethyl 7-alkyl-6-oxo-3-phenyl-6,7-tetrahydrothieno[2,3-b]pyridine-2-carboxylates

The compounds of the following Examples 46-56 were prepared by parallel synthesis using a Radleys Carousel reaction station (Radleys Ltd., Saffron Walden, U.K.) following a procedure similar to that described for Example 2.

Each reaction tube in the Carousel was charged with the appropriate alkyl or arylalkyl halide (1.5mmol, 1.5equiv.), Intermediate 4 (200mg, 0.67mmol), polystyrene supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP, 364mg, 0.8mmol, 1.2equiv.) and a magnetic stirrer bar. Anhydrous DMF (4mL) was added to each tube and the reactions stirred at 65° under nitrogen for 48h. Each reaction was partitioned between water and DCM and the combined DCM extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified on silica eluting with 0-20% EtOAc in DCM to give the title compounds as solids.

Example 46

Ethyl 7-(cyclohexylmethyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.40-7.35 (3H, m), 7.27-7.24 (3H, m), 6.42 (1H, d, J 10Hz), 4.12 (2H, q, J 7Hz), 3.95 (2H, d, J 7.5Hz), 2.08-2.05 (1H, m), 1.67-1.53 (5H, m), 1.16-1.09 (5H, m), 1.11 (3H, t, J 7Hz). LCMS (ES^+) RT 5.17 minutes, 396 $(M+H)^+$.

Example 47

Ethyl 6-oxo-7-(1-phenylethyl)-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.30-7.18 (11H, m), 6.72 (1H, m), 6.49 (1H, d, J 10Hz), 4.05-3.99 (2H, m), 1.91 (3H, d, J 7Hz), 1.01 (3H, t, J 7Hz). LCMS (ES^+) RT 4.29 minutes, 404 $(M+H)^+$.

Example 48

Ethyl 7-(3-methoxybenzyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.40-7.35 (3H, m), 7.29 (1H, d, J 10Hz), 7.25-7.17 (3H, m), 6.93 (1H, m), 6.90 (1H, bs), 6.77 (1H, m), 6.50 (1H, d, J 10Hz), 5.30 (2H, s), 4.08

(2H, q, J 7Hz), 3.72 (3H, s), 1.07 (3H, t, J 7Hz). LCMS (ES^+) RT 4.09 minutes, 420 $(M+H)^+$.

Example 49

Ethyl 7-(2,6-difluorobenzyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

δH ($CDCl_3$) 7.41-7.35 (3H, m), 7.29-7.15 (4H, m), 6.85 (2H, t, J 8Hz), 6.45 (1H, d, J 10Hz), 5.45 (2H, s), 4.08 (2H, q, J 7Hz), 1.06 (3H, t, J 7Hz). LCMS (ES^+) RT 4.06 minutes, 426 $(M+H)^+$.

Example 50

Ethyl 7-(3-methylbutyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.64 minutes, 370 $(M+H)^+$.

Example 51

Ethyl 7-allyl-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.84 minutes, 340 $(M+H)^+$.

Example 52

Ethyl 6-oxo-7-(2-phenylethyl)-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 3.45 minutes, 404 $(M+H)^+$.

Example 53

Ethyl 7-(2-chlorobenzyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.40 minutes, 424 $(M+H)^+$.

Example 54

Ethyl 7-(3-chlorobenzyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.45minutes, 424 $(M+H)^+$.

Example 55

Ethyl 7-(4-chlorobenzyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

LCMS (ES^+) RT 4.49 minutes, 424 $(M+H)^+$.

Example 56

Ethyl 7-(2-morpholinoethyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

This compound was purified by chromatography on silica eluting with 0-20% THF in DCM. LCMS (ES^+) RT 2.52 minutes, 413 $(M+H)^+$.

Example 57

Ethyl 7-(4-bromophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To an oven dried flask was added in sequence 4-bromophenylboronic acid (5.0g, 25mmol), DCM (100mL), pyridine (2.7mL), Intermediate 4 (3.74g, 12.5mmol), copper(II) acetate (2.26g, 12.5mmol) and pyridine N-oxide (1.46g). The reaction was stirred at room temperature for 72h with the exclusion of moisture. The reaction was then diluted with DCM (100mL), washed with 2M HCl(aq), $NaHCO_3$ (aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-20% EtOAc in DCM) to give the title compound as a white solid (2.03g). δH (DMSO-d6) 7.89 (2H, J 8.7Hz), 7.58 (2H, J 8.7Hz), 7.53-7.49 (3H, m), 7.46 (1H, d, J 9.7Hz), 7.42-7.40 (2H, m), 6.57 (1H, d, J 9.7Hz), 4.07 (2H, q, J 7.1Hz), 1.06 (3H, t, J 7.1Hz). LCMS (ES^+) RT 4.25 minutes, 456 $(M+H)^+$.

Example 58

Ethyl 7-(4-morpholinophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a mixture of the compound of Example 57 (100mg, 0.22mmol), caesium carbonate (101mg, 0.31mmol), $Pd(OAc)_2$ (5mg, 0.022mmol, 10mol%) and 2,2'-bis(diphenylphosphino)-1-1'-binaphthyl (BINAP) (21mg, 0.033mmol, 15mol%) in toluene (2mL) and under nitrogen was added morpholine (0.024mL, 0.27mmol). The reaction mixture was heated to 100° for 18h. Solvent was removed *in vacuo* and the crude product purified by chromatography on silica (0-20%THF in DCM) to give the title compound as a white solid (40mg).

δH ($CDCl_3$) 7.50-7.18 (8H, m), 7.01 (2H, d, J 9Hz), 6.52 (1H, d, J 10Hz), 4.06 (2H, q, J 7Hz), 3.82 (4H, m), 3.22 (4H, m), 1.06 (3H, t, J 7Hz). LCMS (ES^+) RT 3.82 minutes, 461 $(M+H)^+$.

Example 59

6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

To a solution of the compound of Example 1 (4.53g, 12.1mmol) in 2:1 THF-water (150mL) was added $LiOH.H_2O$ (1.50g, 36.2mmol) and the reaction stirred for 36h at r.t. The reaction was diluted with water 50mL and 2M HCl(aq) added with stirring until a precipitate had formed (pH 1-2). The solid was filtered, washed with several portions of water and dried in a vacuum oven (50°C) to afford the title compound as a white solid (4.2g). δH (DMSO-d6) 13.00 (1H, bs), 7.70-7.40 (11H, m), 6.55 (1H, d, J 10Hz). LCMS (ES^+) RT 3.10 minutes, 348 $(M+H)^+$.

Example 60

2-[(4-Methylpiperazino)carbonyl]-3,7-diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one

To a suspension of the compound of Example 59 (100mg, 0.29mmol) in DCM (2mL) was added EDC (67mg, 0.348mmol) and HOBT (43mg, 0.32mmol) and the mixture stirred at r.t. for 15 minutes. A solution N-methyl piperazine (28mg, 0.32mmol) in DCM (0.5mL) was added and the reaction stirred at r.t. for 18h. The reaction mixture was diluted with DCM (10mL), washed with water (2x5mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-20%THF in DCM) to give the title compound as an off-white solid (82mg). δH (DMSO-d6) 7.67 (1H, dd, J 10, 1Hz), 7.62-7.52 (3H, m), 7.51-7.40 (5H, m), 7.35-7.31 (2H, m), 6.51 (1H, dd, J 10, 1Hz), 2.44 (8H, m), 1.88 (3H, s). LCMS (ES^+) RT 2.18 minutes, 430 $(M+H)^+$.

Example 61

***N*-Ethyl-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

EDC (66mg, 0.35mmol) and HOBT (43mg, 0.32mmol) were added to the compound of Example 59 (100mg, 0.29mmol) in DCM (2mL). After 15min ethylamine hydrochloride (26mg, 0.32mmol) and NMM (0.070mL, 0.63mmol) were added and the reaction mixture was stirred at r.t. overnight. Water (2mL) and DCM (2mL) were added, the suspension filtered through a hydrophobic frit and the organic phase concentrated *in vacuo*. The crude product was purified by column chromatography on silica (1% MeOH in DCM) to give the title compound as a white solid (95mg, 88%). δH (DMSO-d6) 7.69-7.61 (3H, m), 7.59-7.49 (3H, m), 7.45 (1H, d, J 9.6Hz), 7.44-7.42 (4H, m), 7.05 (1H, t, J 5.4Hz), 6.54 (1H, d, J 9.6Hz), 3.03 (2H, q, J 7.1Hz), 0.84 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.33 minutes, 375.0 $(M+H)^+$.

The following compounds of Examples 62-74 were prepared from the compound of Example 59 and the appropriate amine or amine hydrochloride by the method of Example 61.

Example 62

N-(3-Hydroxypropyl)-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

LCMS (ES^+) RT 2.99 minutes, 405.0 $(M+H)^+$

Example 63

6-Oxo-3,7-diphenyl-N-[2-(1-pyrrolidinyl)ethyl]-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

LCMS (ES^+) RT 2.29 minutes, 444.1 $(M+H)^+$

Example 64

6-Oxo-3,7-diphenyl-N-(2-piperidinoethyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

LCMS (ES^+) RT 2.33 minutes, 458.1 $(M+H)^+$

Example 65

N-(3-Methoxypropyl)-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

LCMS (ES^+) RT 3.28 minutes, 419.0 $(M+H)^+$

Example 66

N-(2-Methoxyethyl)-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

LCMS (ES^+) RT 3.24 minutes, 405.0 $(M+H)^+$

Example 67

3,7-Diphenyl-2-(1-pyrrolidinylcarbonyl)thieno[2,3-*b*]pyridin-6(7*H*)-one

LCMS (ES^+) RT 3.43 minutes, 401.0 $(M+H)^+$

Example 68

***N*-[3-(1*H*-Imidazol-1-yl)propyl]-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 2.28 minutes, 455.1 $(M+H)^+$

Example 69

***N*-(2-Morpholinoethyl)-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 2.28 minutes, 460.1 $(M+H)^+$

Example 70

***N*-[3-(4-Methylpiperazino)propyl]-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 2.16 minutes, 487.1 $(M+H)^+$

Example 71

***N*-(3-Morpholinopropyl)-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 2.26 minutes, 474.1 $(M+H)^+$

Example 72

***N,N*-Diethyl-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 3.62 minutes, 403.0 $(M+H)^+$

Example 73

***N,N*-Dimethyl-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 3.17 minutes, 375.0 $(M+H)^+$

Example 74

***N*-Methyl-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

LCMS (ES^+) RT 3.15 minutes, 361.0 $(M+H)^+$

Example 75

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

1,1'-Carbonyldiimidazole (51mg, 0.32mmol) was added to the compound of Example 59 (100mg, 0.29mmol) in DMF (2mL). After 15 min aq. ammonia (0.190 mL, 25% solution, 3.0mmol) was added and the solution stirred at r.t. overnight. The mixture was concentrated *in vacuo* and azeotroped twice with heptane. The crude product was purified by column chromatography on silica (3% MeOH in DCM) to give the title compound as a white solid (74mg, 74%). δH (DMSO-d6) 7.87-7.76 (3H, m), 7.75-7.68 (5H, m), 7.64-7.61 (2H, m), 7.54 (1H, d, J 9.6Hz), 6.69 (1H, d, J 9.6Hz), 6.25 (2H, br s). LCMS (ES^+) RT 2.95 minutes, 347.0 $(M+H)^+$.

Example 76

***N*-Methoxy-*N*-methyl-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

N,O-Dimethylhydroxylamine hydrochloride (31mg, 0.32mmol) was added to a mixture of the compound of Example 59 (101mg, 0.29mmol), HOBT (55mg, 0.41mmol), EDC (78mg, 0.41mmol) and NMM (0.090mL, 0.81mmol) in DCM (3mL). The mixture was stirred for 6h at room temperature. DCM was added and the mixture washed with 2M HCl(aq). The organic phase was re-extracted with DCM. The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (3.5% MeOH in DCM) to give the title compound as a white solid (95mg, 84%). δH (DMSO-d6) 7.48-7.35 (3H, m), 7.34-7.30 (3H, m), 7.29-7.23 (3H, m), 7.16-7.13 (2H, m), 6.33 (1H, d, J 9.6Hz), 3.26 (3H, s), 2.79 (3H, s). LCMS (ES^+) RT 3.27 minutes, 391.0 $(M+H)^+$.

Example 77

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

A mixture of cyanuric chloride (28mg, 0.15mmol) and the compound of Example 75 (52mg, 0.15mmol) in DMF (1.5mL) was heated at 110° for 18h. Two further portions of cyanuric chloride (14mg, 0.075mmol) were added and heating continued for a further 26h. Water was added and the precipitate filtered off, washed with water and dried. The crude product was purified by column chromatography on silica (1% THF in DCM) to give the <u>title compound</u> as a white solid (35mg, 71%). δH (DMSO-d6) 7.78 (1H, d, <u>J</u> 9.6Hz), 7.71-7.67 (1H, m), 7.66-7.64 (1H, m), 7.64-7.59 (7H, m), 7.59-7.58 (1H, m), 6.67 (1H, d, <u>J</u> 9.6Hz). LCMS (ES^+) RT 3.65 minutes, 329 $(M+H)^+$.

<u>Example 78</u>

<u>2-(1-Hydroxy-1-methylethyl)-3,7-diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one</u>

A solution of methyl magnesium iodide (0.084 mL of a 3M solution in ether, 0.25mmol) was added drop-wise to a solution of the compound of Example 1 (47mg, 0.13mmol) in DCM (2mL) at 0°. The mixture was allowed to warm to r.t. and stirred for 18h. More methyl magnesium iodide (0.084 mL of a 3M solution in ether, 0.25mmol) was added at 0° and the mixture stirred at r.t. for 1h. DCM and NH_4Cl(aq) were added, the aqueous phase re-extracted with DCM and the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (1% MeOH in DCM) to give the <u>title compound</u> as a yellow solid (36mg, 80%). δH (DMSO-d6) 7.74-7.64 (3H, m), 7.60-7.52 (5H, m), 7.39 (2H, dd, <u>J</u> 7.8, 1.6Hz), 7.10 (1H, d, <u>J</u> 9.5 Hz), 6.45 (1H, d, <u>J</u> 9.5Hz), 2.58 (6H, s). LCMS (ES^+) RT 3.46 minutes, 362 $(M+H)^+$.

<u>Example 79</u>

<u>2-(Hydroxymethyl)-3,7-diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one</u>

Lithium borohydride (0.100mL, 2M in THF, 0.2mmol) was added to a solution of the compound of Example 1 (75mg, 0.198mmol) in THF (2mL) and the reaction mixture was stirred at r.t. overnight. Two further portions of lithium

borohydride (0.100mL, 2M in THF, 0.198mmol) were added and the mixture stirred for a further 6h. The reaction was quenched by the addition of 2M HCl(aq) and the mixture neutralised by the addition of Na_2CO_3 The resulting precipitate was filtered off, washed with water and dried to give the title compound as a white solid (55mg, 97%). δH (DMSO-d6) 7.68-7.41 (11H, m), 6.49 (1H, d, J 9.5Hz), 5.57 (1H, br s), 4.50 (2H, br s). LCMS (ES^+) RT 3.10 minutes, 334.0 $(M+H)^+$.

Example 80

tert-Butyl *N*-(6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)carbamate

Triethylamine (0.076mL, 0.55mmol) and diphenylphosphoryl azide (0.119mL, 0.55mmol) were added to a solution of the compound of Example 59 (174mg, 0.5mmol) in dry *tert*-butanol (5mL) and the mixture heated under reflux under nitrogen for 6h. The cooled mixture was poured into saturated $NaHCO_3$(aq) (20mL) and extracted with DCM (2 x 20mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica (EtOAc) to give the title compound (196mg, 94%). δH ($CDCl_3$) 7.5-7.25 (11H, m), 6.70 (1H, br s), 6.46 (1H, d, J 9Hz), 1.29 (9H, s). *m/z* (ES^+) 419 $(M+H)^+$.

Example 81

2-Amino-3,7-diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one

Trifluoroacetic acid (2mL) was added to a solution of the compound of Example 80 (170mg, 0.406mmol) in DCM (2mL) and the reaction mixture stirred for 2h at r.t.. The mixture was added to saturated $NaHCO_3$(aq) (20mL) and the product extracted with DCM (2 x 20mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica (EtOAc), followed by radial chromatography (20%EtOH in DCM) to give the title

compound as a buff solid (30mg, 23%). δH ($CDCl_3$) 7.8-7.3 (13H, m), 6.58 (1H, d, J 9Hz). *m/z* (ES^+) 319 $(M+H)^+$.

Example 82

***tert*-Butyl *N*-methylsulfonyl-*N*-(6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)carbamate**

Sodium bis(trimethylsilyl) amide (0.25mL of a 1M solution in THF, 0.25mmol) was added to a solution of the compound of Example 80 (105mg, 0.25mmol) in dry THF (5mL) under a nitrogen atmosphere at 0°. After 30min methane sulfonyl chloride (28.6mg, 0.25mmol) was added. The reaction mixture was allowed to warm to r.t. over 1h then poured into saturated $NaHCO_3$(aq) (20mL) and the product extracted with DCM (2 x 20mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude product was purified by radial chromatography on silica (EtOAc) to give the title compound (115mg, 92%). δH ($CDCl_3$) 7.6-7.28 (11H, m), 6.55 (1H, d, J 9Hz), 2.68 (3H, s), 1.32 (9H, s). *m/z* (ES^+) 497 $(M+H)^+$.

Example 83

***N*-(6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)methanesulfonamide**

Trifluoroacetic acid (2.5mL) was added to a solution of the compound of Example 82 (105mg, 0.212mmol) in DCM (2.5mL) and the reaction mixture stirred for 2h at r.t.. The mixture was added to saturated $NaHCO_3$ solution (20mL) and the product extracted with DCM (2 x 20mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude product was purified by radial chromatography on silica (EtOAc) to give the title compound (62mg, 74%). δH ($CDCl_3$) 7.6-7.25 (11H, m), 6.58 (1H, d, J 9Hz), 6.31 (1H, br s), 2.53 (3H, s). *m/z* (ES^+) 397 $(M+H)^+$.

Example 84

3,7-Diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one

2M HCl(aq) (10mL) was added to a solution of the compound of Example 59 (300mg, 0.864mmol) in dioxane (30mL) and the mixture heated at reflux for 16h. The cooled reaction mixture was poured into 10% NaOH(aq) (50mL) and extracted with DCM (2 x 50mL) The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound as a white solid in quantitative yield. δH ($CDCl_3$) 7.83 (1H, d, J 9Hz), 7.7-7.35 (10H, m), 6.80 (1H, s), 6.67 (1H, d, J 9Hz). *m/z* (ES^+) 304 $(M+H)^+$.

Example 85

N-(6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)acetamide

Acetyl chloride (0.10mL) was added to a solution of the compound of Example 81 (116mg, 0.38mmol) and pyridine (0.10mL) in DCM (5mL) and the mixture stirred at r.t. overnight. The reaction was quenched with MeOH and partitioned between DCM and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by column chromatography on silica (0-5% MeOH in EtOAc) to give the title compound (39mg, 21%). δH($CDCl_3$) 7.65 (1H, br s), 7.63-7.39 (11H, m), 6.63 (1H, d, J 9.5Hz), 1.99 (3H, s). LCMS (ES^+) RT 2.621 minutes, 361 $(M+H)^+$.

Example 86

1-Methyl-*N*-(6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-1*H*-imidazole-4-sulfonamide

1-Methyl-1*H*-imidazole-4-sulfonyl chloride (96mg, 0.53mmol) was added to a solution of the compound of Example 81 (136mg, 0.44mmol) and pyridine (52mg, 0.66mmol) in DCM (10mL) and the reaction mixture stirred at r.t. overnight. The mixture was partitioned between DCM and $NaHCO_3$(aq). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by column chromatography on silica (10%MeOH in DCM) to give the title compound (75mg, 37%). δH (MeOH-d4) 7.60-7.48 (5H,

m), 7.38-7.25 (6H, m), 7.23 (1H, m), 7.13 (2H, m), 6.48 (1H, d, J 9.5Hz), 3.55 (3H, s). LCMS (ES^+) RT 2.90 minutes, 463 $(M+H)^+$.

Example 87

Ethyl 7-[4-(benzyloxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 4 (2.50g, 8.36mmol), 4-(benzyloxy)phenylboronic acid (2.86g, 12.5mmol), copper(II) acetate (3.04g, 16.7mmol) and pyridine (2.7mL, 33.4mmol) in DCM (200mL) was stirred at r.t. for 5 days. The mixture was diluted with DCM (100mL) and filtered through celite. The filtrate was washed with 2M HCl(aq) (2 x 200mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (3% MeOH in DCM) to give the title compound as a white solid (1.35g, 34%). δH ($CDCl_3$) 7.52-7.35 (13H, m), 7.21-7.16 (2H, m), 6.60 (1H, d, J 9.6Hz), 5.15 (2H, s), 4.14 (2H, q, J 7.1Hz), 1.13 (3H, t, J 7.1Hz). *m/z* (ES^+) 482.1 $(M+H)^+$.

Example 88

Ethyl 7-[4-(hydroxymethyl)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 4 (300mg, 1.0mmol), 4-(hydroxymethyl)phenyl boronic acid (304mg, 12.5mmol), copper(II) acetate (913mg, 5.0mmol) and pyridine (0.404mL, 5.0mmol) in DCM (7mL) was stirred at r.t. for 3 days. The mixture was diluted with DCM, washed with HCl (2M), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (50-100% EtOAc in isohexane) to give the title compound as a white solid (255mg, 63%). δH ($CDCl_3$) 7.54 (2H, d, J 8.9Hz), 7.44-7.28 (8H, m), 6.53 (1H, d, J 10.6Hz), 4.72 (2H, s), 4.06 (2H, q, J 7.1Hz), 1.05 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.45 minutes, 406 $(M+H)^+$.

Example 89

Ethyl 7-(4-hydroxyphenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 4 (554mg, 1.86mmol), 4-hydroxyphenyl boronic acid (511mg, 3.71mmol), copper(II) acetate (37mg, 0.187mmol), pyridine-*N*-oxide (350mg, 3.71mmol) and pyridine (0.370mL, 3.71mmol) in DCM (20mL) was stirred at r.t. overnight. The reaction mixture was diluted with DCM, washed with NH_4Cl(aq) and water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (5% MeOH in DCM) to give the title compound as a cream solid (484mg, 73%). δH (DMSO-d6) 10.06 (1H, s), 7.54-7.50 (3H, m), 7.47-7.45 (3H, m), 7.37 (2H, d, J 9Hz), 7.02 (2H, d, J 9Hz), 6.58 (1H, d, J 10Hz), 4.11 (2H, q, J 7Hz), 1.09 (3H, t, J 7Hz). LCMS (ES^+) 392.1 $(M+H)^+$.

Example 90

Ethyl 7-[4-(2-hydroxyethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

2-Bromoethanol (0.148mL, 2.08mmol) was added to the compound of Example 89 (370mg, 0.95mmol) and Cs_2CO_3 (342mg, 1.04mmol) in DMF (5mL) and the mixture heated at 80° for 2 days. The solvent was removed *in vacuo* and the residue partitioned between EtOAc and HCl (10%). The aqueous phase was extracted with EtOAc (2 x 20mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (2% to 10% MeOH in DCM) to give the title compound (73mg, 18%). δH ($CDCl_3$) 7.44-7.28 (8H, m), 7.07 (2H, d, J 8Hz), 6.52 (1H, d, J 9.6Hz), 4.12-3.93 (6H, m), 1.06 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.42 minutes, 436 $(M+H)^+$.

Example 91

Ethyl 7-{4-[2-(2-methyl-1*H*-imidazol-1-yl)ethoxy]phenyl}-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Pyridine (0.136mL, 1.68mmol) was added to a mixture of the compound of Example 90 (73mg, 0.168mmol) and tosylchloride (40mg, 0.21mmol) in DCM (2mL) at 0°. The reaction mixture was stirred at 0° for 5h then allowed to warm to r.t. The mixture was diluted with DCM (20mL), washed with 2M HCl(aq), 10% NaOH(aq) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (50 to 80% EtOAc in isohexane) to give the intermediate tosylate, ethyl 7-[4-(2-[(4-methylphenyl)sulfonyl]oxyethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydro-1-benzothiophene-2-carboxylate, as a solid (73mg, 12%). δH($CDCl_3$) 7.78 (2H, d, J 8.6Hz), 7.43-7.27 (10H, m), 6.93 (2H, d, J 8.6Hz), 6.52 (1H, d, J 9.6Hz), 4.38-4.35 (2H, m), 4.18-4.15 (2H, m), 4.07 (2H, q, J 7.1Hz), 2.40 (3H, s), 1.06 (3H, t, J 7.1Hz). LCMS (ES^+) RT 4.15 minutes, 590 $(M+H)^+$.

A mixture of this tosylate (70mg, 0.12mmol), 2-methylimidazole (11mg, 0.13mmol) and Cs_2CO_3 (43mg, 0.13mmol) in DMF (1mL) was heated at 80° for 6h. The solvent was removed *in vacuo* and the residue partitioned between DCM (15mL) and $NaHCO_3$(aq) (15mL). The organic phase was extracted with DCM (2 x 10mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (10% MeOH in DCM) to give the title compound (20mg, 34%). δH($CDCl_3$) 7.43-7.28 (8H, m), 7.19-7.15 (2H, m), 7.01-6.90 (2H, m), 6.51 (1H, d, J 9.6Hz), 4.25-4.20 (4H, br m), 4.06 (2H, q, J 7.1Hz), 2.43 (3H, s), 1.05 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.62 minutes, 500 $(M+H)^+$.

Example 92

Ethyl 7-[4-(2-morpholinoethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a mixture of the compound of Example 89 (100mg, 0.256mmol) and caesium carbonate (202mg, 0.62mmol) in dry DMF (5mL) was added 2-(chloroethyl)morpholine hydrochloride (58mg, 0.31mmol) and the reaction heated at 60° under nitrogen for 48h. The reaction was partitioned between water and EtOAc, the EtOAc extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica eluting with 0-5% MeOH in DCM to give the title compound as a white solid (68mg). δH ($CDCl_3$) 7.44-7.20 (8H, m), 7.04 (2H, d, J 9Hz), 6.51 (1H, d, J 10Hz), 4.15-4.03 (4H, m), 3.68 (4H, m), 2.79 (2H, t, J 6Hz), 2.54 (4H, m), 1.05 (3H, t, J 7Hz). LCMS (ES^+) RT 2.53 minutes, 505 $(M+H)^+$.

Example 93

Ethyl 6-oxo-3,7-diphenyl-4,5,6,7-tetrahydrothieno[2,3-b]pyridine-2-carboxylate

Hydrogen at 20 to 25 bar was applied to a mixture of the compound of Example 1 (185mg), 10% ruthenium on carbon (64mg) and EtOH (25mL) stirred at 60 to 90° for 30 hours. The mixture was filtered to remove the catalyst and the filter was washed with EtOH (70mL). The solution was concentrated *in vacuo* to give a crude product. This was purified by preparative HPLC (0.08% formic acid in acetonitrile, pH2, Luna 2 C18 5μm 250 mm) to give the title compound as a white solid (48mg, 26%). δH ($CDCl_3$) 7.59-7.48 (3H, m), 7.47-7.36 (5H, m), 7.30 (2H, dd, J 8.5, 2.1 Hz), 4.10 (2H, q, J 7.3 Hz), 2.84 (2H, m), 2.75 (2H, m), 1.10 (3H, t, J 7.3 Hz). LCMS RT 4.1 minutes, 378 $(M+H)^+$

Example 94

7-(4-Methoxybenzyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Sodium hydride (24mg of 60% w/w dispersion in oil, 0.6mmol) was added to a solution of Intermediate 12 (126mg, 0.5mmol) in dry DMF (4mL) and stirred

at r.t. for 10 mins under nitrogen. 4-Methoxybenzyl chloride (68µL, 0.5mmol) was added and the reaction mixture heated to 60° for 2 hours. The reaction was allowed to cool to r.t. and was partitioned between EtOAc (75mL) and brine (50mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and the crude product purified by column chromatography (silica, 10% EtOAc in DCM) to give the title compound as a white solid (93mg, 50%). δH ($CDCl_3$) 7.48 (1H, d, J 9.6Hz), 7.42-7.33(5H, m), 7.26 (2H, d, J 8.8Hz), 6.77 (2H, d, J 8.8Hz), 6.55 (1H, d, J 9.6Hz), 5.19 (2H, s), 3.68 (3H, s). LCMS (ES^+) 395 $(M+H)^+$.

Example 95

N-Allyl-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

To a stirred solution of the compound of Example 59 (174mg, 0.5mmol) in dry DCM (5mL) was added allyl amine (29mg, 0.5mmol), triethylamine (101mg, 1mmol), and a catalytic amount of 4-dimethylaminopyridine followed by EDC (96mg, 0.5mmol). The reaction mixture was stirred at r.t. for 4h and then poured into 2M HCl(aq) (20mL). The product was extracted with DCM (2x20mL) and the combined organic fractions dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by radial chromatography (silica, EtOAc) gave the title compound as a solid (70mg). δH ($CDCl_3$) 7.7-7.1 (11H, m), 4.48 (1H, d, J 10Hz), 5.6-5.4 (1H, m), 5.28 (1H, bs), 4.84 (1H, dd, J 10, 1Hz), 4.69 (1H, dd, J 10, 1Hz), 3.8-3.6 (2H, m). LCMS (ES^+) 387 $(M+H)^+$.

Example 96

N-(2,3-dihydroxypropyl)-6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

To a stirred solution of the compound of Example 95 (50mg) in 8:1 acetone-water (10mL) was added 4-methylmorpholine N-oxide (100mg) followed by a catalytic amount of OsO_4. The reaction mixture was stirred for 16h and then

poured into saturated $NaHCO_3$ solution (20mL). The product was extracted with DCM (2x20mL) and the combined organic fractions dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by column chromatography (silica, 10% EtOH in DCM) to give the title compound as a solid (32mg). δH ($CDCl_3$) 7.8-7.1 (11H, m), 6.44 (1H, d, J 10Hz), 5.62 (1H, bs), 3.7-3.1 (5H, m). LCMS (ES^+) 421 $(M+H)^+$.

Example 97

(6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-urea

To a stirred solution of the monohydrochloride salt of the compound of Example 81 (0.177g, 0.5mmol) in dry pyridine (5mL) was added excess trimethylsilyl isocyanate and the reaction stirred at r.t. for 16h. The reaction was poured onto 2M HCl(aq) (20mL) and extracted with DCM (2x20mL). The combined organic fractions were dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by radial chromatography (silica, EtOAc) to give the title compound as a solid (6mg). δH (DMSO-d6) 8.78 (1H, s), 7.8-7.55 (5H, m), 7.5-7.4 (6H, m), 6.48 (1H, d, J 10Hz), 6.32 (2H, bs). LCMS (ES^+) 362 $(M+H)^+$.

Example 98

1-Ethyl-3-(6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-urea

The title compound was prepared from the HCl salt of the compound of Example 81 and ethyl isocyanate following the method described for the compound of Example 97 to give the product as a solid (24mg). δH (DMSO-d6) 8.59 (1H,s), 7.8-7.4 (11H, m), 6.67 (1H, t, J 5Hz), 6.38 (1H, d, J 10Hz), 3.1-2.9 (2H, m), 0.97 (3H, t, J 7Hz). LCMS (ES^+) 390 $(M+H)^+$.

Example 99

1-(2-Hydroxyethyl)-3-(6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-urea

To a stirred suspension of the monohydrochloride salt of the compound of Example 81 (177mg, 0.5mmol) in dry DCM was added phosgene (0.26mL of 1.93M solution in toluene, 0.5mmol), followed by triethylamine (101mg, 1.0mmol). The reaction was stirred for 1h at r.t. before adding more triethylamine (51mg, 0.5mmol) and ethanolamine (31mg, 0.5mmol). The reaction was stirred for a further hour and then poured into saturated

$NaHCO_3$(aq) (20mL). The product was extracted with DCM (2x20mL), the combined organic fractions dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by radial chromatography (silica, EtOAc) to give the title compound as a solid (34mg). δH (DMSO-d6) 8.84 (1H,s), 7.8-7.3 (11H, m), 6.85 (1H, t, J 5Hz), 6.41 (1H, d, J 10Hz), 4.69 (1H, t, J 5Hz), 3.4-3.2 (2H, m), 3.1-2.9 (2H, m). LCMS (ES^+) 406 $(M+H)^+$.

Example 100

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-sulfonic acid methylamide

To a solution of Intermediate 13 (32mg, 0.085mmol) in DCM (5mL) was added methylamine (40% solution in water, 0.17mmol, 0.1mL) and the reaction stirred at r.t. for 18h. The reaction was partitioned between DCM and saturated $NaHCO_3$(aq) and the DCM layer dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, EtOAc) to give the title compound as an off-white solid (10mg). δH ($CDCl_3$) 7.71 (2H, dt, J 8.5, 1.8Hz), 7.73 (1H, d, J 9.6Hz), 7.48-7.62 (5H, m), 7.40 (2H, m), 6.86 (1H, s), 6.63 (1H, d, J 9.6Hz), 4.41 (1H, q, J 5.3Hz), 2.68 (3H, d, J 5.3Hz). LCMS (ES^+) RT 3.14 minutes, 397 $(M+H)^+$.

Example 101

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-sulfonic acid pyrrolidine amide

The title compound was prepared from Intermediate 13 (18mg) and pyrrolidine (0.1mL) following the method described for the compound of Example 100 to give the product as an off-white solid (4mg). δH ($CDCl_3$) 7.89 (2H, m), 7.74 (1H, d, J 9.6Hz), 7.48-7.60 (5H, m), 7.40 (2H, m), 6.87 (1H, s), 6.64 (1H, d, J 9.6Hz), 3.24 (4H, m), 1.77 (4H, m). LCMS (ES^+) RT 3.47 minutes, 437 $(M+H)^+$.

Example 102

7-[4-(2-Morpholinoethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine

The compound of Example 92 (91mg, 0.18mmol) was dissolved in dioxane (1mL) and 4M HCl(aq) (1mL) added and the mixture heated at reflux for 48h. The reaction was partitioned between 2M NaOH(aq) and THF and the combined THF layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 0-10% MeOH in EtOAc) to give the title compound as an off-white solid (73mg, 94%). δH ($CDCl_3$) 7.74 (1H, d, J 9.6Hz), 7.33-7.28 (7H, m), 7.05-7.01 (2H, m), 6.75 (1H, s), 6.58 (1H, d, J 9.6Hz), 4.12 (2H, t, J 5.7Hz), 3.76-3.67 (4H, m), 2.78 (2H, t, J 5.7Hz), 2.56-2.52 (4H, m). LCMS (ES^+) RT 2.46 minutes, 433 $(M+H)^+$.

Example 103

7-[4-(2-Morpholinoethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

A mixture of the compound of Example 92 (230mg, 0.46mmol), sodium hydroxide (91mg, 2.28mmol) and EtOH (5mL) was heated at reflux for 18h. EtOH was removed *in vacuo* and the residue treated with 2M HCl(aq) (2mL) to give a white solid. The reaction was diluted with water and then freeze dried. The resultant solid was extracted with isopropanol and the extracts concentrated *in vacuo* to give the title compound as a white solid (97mg). δH (DMSO-d6) 7.62-7.37 (8H, m), 7.21-7.16 (2H, m), 6.50 (1H, J 9.6Hz), 4.20 (2H, t, J 5.7Hz), 3.62-3.59 (4H, m), 2.76 (2H, t, J 5.7Hz), 2.54-2.51 (4H, m). LCMS (ES^+) RT 2.35 minutes, 477 $(M+H)^+$.

Example 104

7-[4-(2-Morpholinoethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

To a suspension of the compound of Example 103 (120mg, 0.25mmol) in dry DMF (3mL) was added 1,1'-carbonyldiimidazole (41mg) and the reaction stirred for 1h. A further portion of 1,1'-carbonyldiimidazole (5mg) was added and the reaction stirred for 30mins before adding aqueous ammonia (1.5mL of 25% solution). The reaction was stirred for 2h and then was diluted with water (20mL). The product was extracted with EtOAc (2x15mL) and the combined organic extracts washed with water (x2), brine (x2) and dried over $MgSO_4$. Solvent was removed *in vacuo* to give the title compound as a solid (128mg). δH ($CDCl_3$) 7.52-7.49 (3H, m), 7.40-7.18 (5H, m), 7.10-7.00 (2H, m), 6.51 (1H, d, J 9.6Hz), 5.34 (2H, bs), 4.12 (2H, t, J 5.7Hz), 3.71-3.67 (4H, m), 2.79 (2H, t, J 5.7Hz), 2.56-2.53 (4H, m). LCMS (ES^+) RT 2.28 minutes, 476 $(M+H)^+$.

Example 105

7-[4-(2-Morpholinoethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

To a solution of the compound of Example 104 (128mg, 0.27mmol) in dry DCM (1.5mL) was added pyridine (44μL, 0.54mmol) followed by trifluoroacetic anhydride (46μL, 0.32mmol). TLC showed the reaction was complete after 5 minutes and the reaction was then diluted with DCM (20mL) and washed with 2M NaOH(aq) (20mL). The DCM layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was co-evaporated with toluene (2x15mL) to give the title compound as a solid (73mg). δH ($CDCl_3$) 7.62 (1H, d, J 9.7Hz), 7.51-7.45 (5H, m), 7.29-7.26 (2H, m), 7.08-7.04 (2H, m), 6.62 (1H, d, J 9.7Hz), 4.14 (2H, t, J 5.6Hz), 3.71-3.68 (4H, m), 2.81 (2H, t, J 5.6Hz), 2.58-2.54 (4H, m). LCMS (ES^+) RT 2.47 minutes, 458 $(M+H)^+$.

Example 106

Ethyl 7-[4-(2,3-dihydroxypropoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of the compound of Example 89 (680mg, 1.74mmol), 2,2-dimethyl-1,3-dioxalan-4-ylmethyl *p*-toluenesulfonate (600mg, 2.09mmol), and caesium carbonate (680mg, 2.09mmol) in DMF (3mL) was heated at 80° for 18h. The reaction mixture was cooled and then partitioned between DCM (30mL) and water (30mL). The aqueous layer was extracted with two further portions of DCM (10mL) and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 10-15% EtOAc in DCM) to give ethyl 7-[4-(2,2-dimethyl-[1,3]dioxan-4-ylmethoxy)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate as a white solid (474mg, 54%). δH ($CDCl_3$) 7.52-7.43 (8H, m), 7.25-7.20 (2H, m), 6.67 (1H, d, J 9.6Hz), 4.66-4.58 (1H, m), 4.32-4.01 (5H, m), 1.58 (3H, s), 1.51 (3H, s), 1.22 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.99 minutes, 505 $(M+H)^+$. This intermediate (450mg) was dissolved in EtOH (10mL) and a catalytic amount of Dowex® 50WX4-200 resin in H^+ form was added followed by water (1mL). The reaction was heated at 50° overnight and then diluted with EtOH (10mL) and filtered hot to remove Dowex® resin. The filtrate was concentrated *in vacuo* to give the title compound as an off-white solid (388mg). δH ($CDCl_3$) 7.60-7.38 (8H, m), 7.27-7.24 (2H, m), 6.72 (1H, d, J 9.6Hz), 6.30-4.23 (5H, m), 4.03-3.89 (2H, m), 1.26 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.18 minutes, 488 $(M+Na)^+$, 466 $(M+H)^+$.

Example 107

7-{4-[2-(2-Methyl-1*H*-imidazol-1-yl)ethoxy]phenyl}-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

To a solution of the compound of Example 91 (134mg, 0.27mmol) in EtOH (0.5mL) and water (0.73mL) was added sodium hydroxide (0.27mL of a 1M solution, 0.27mmol) and the mixture heated at reflux for 5h. The reaction was freeze dried to give 7-{4-[2-(2-Methyl-1*H*-imidazol-1-yl)ethoxy]phenyl}-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid as a solid. LCMS (ES^+) RT 2.34 minutes, 472 $(M+H)^+$. This compound was dissolved in DMF (2mL) and thionyl chloride (30μL, 0.405mmol) was added and the reaction stirred at r.t. for 5 mins. Aqueous ammonia (2mL of a 25% solution) was added and the reaction stirred for 30 mins. The reaction was diluted with water (20mL) and extracted with EtOAc (3x30mL). The combined EtOAc extracts were washed with water (2x10mL), brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a solid (104mg, 82%). δH ($CDCl_3$) 7.52-7.48 (3H, m), 7.37-7.33 (2H, m), 7.29-7.26 (2H, m), 7.20-7.18 (1H, m), 7.01-6.96 (3H, m), 6.90-6.88 (2H, m), 6.50 (1H, d, J 9.6Hz), 4.23-4.20 (4H, m), 2.42 (3H, s). LCMS (ES^+) RT 2.28 minutes, 471 $(M+H)^+$.

Example 108

7-{4-[2-(2-Methyl-1*H*-imidazol-1-yl)ethoxy]phenyl}-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

To a suspension of the compound of Example 107 (93mg, 0.20mmol) and pyridine (32μL, 0.4mmol) in DCM (1mL) was added trifluoroacetic anhydride (34μL, 0.24mmol) and the reaction stirred at r.t. for 30 mins. A further 60μL of trifluoroacetic anhydride was added and the reaction stirred for 18h before being diluted with DCM (10mL) and THF (5mL). The mixture was washed with 2M NaOH(aq), brine and the organic layer separated and dried over $MgSO_4$. Solvent was removed *in vacuo* and the residue purified by column chromatography (silica, 2-5% MeOH in DCM) to give the title compound as a solid (60mg, 67%). δH ($CDCl_3$) 7.62 (1H, d, J 9.7Hz), 7.51-7.44 (5H, m), 7.30-7.27 (2H, m), 7.01-6.98 (2H, m), 6.89 (2H, d, J 0.9Hz), 6.61 (1H, d, J

9.7Hz), 4.30-4.20 (4H, m), 2.43 (3H, s). LCMS (ES^+) RT 2.46 minutes, 453 $(M+H)^+$.

Example 109

7-{4-[2-(2-Methyl-1*H*-imidazol-1-yl)ethoxy]phenyl}-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine

To a solution of the compound of Example 91 (60mg, 0.12mmol) in dioxane (1mL) was added 4M HCl(aq) (1mL) and the mixture heated at reflux for 48h. Reaction was diluted with 2M NaOH(aq) (5mL) and extracted with DCM (2x10mL). The combined DCM extracts were dried (MgSO4), filtered and concentrated *in vacuo*. The resultant solid was dried at 60° in a vacuum oven to afford the title compound (32mg, 62%). δH ($CDCl_3$) 7.76 (1H, d, J 9.6Hz), 7.42-7.30 (6H, m), 7.00-6.92 (4H, m), 6.76 (1H, s), 6.58 (1H, d, J 9.6Hz), 4.26-4.20 (4H, m), 2.46 (3H, s). LCMS (ES^+) RT 2.48 minutes, 428 $(M+H)^+$.

Example 110

Ethyl 7-[4-(2-methyl-1*H*-imidazol-1-ylmethyl)phenyl]-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a suspension of the compound of Example 88 (130mg, 0.32mmol) in THF (2mL) was added NaH (14mg of 60% dispersion in oil, 0.35mmol). DMF (0.5mL) was added to aid solubility and the reaction was stirred for 1h. Thionyl chloride (25μL, 0.35mmol) was added to the reaction mixture cooled in an ice-bath. The mixture was stirred in the ice-bath for 30 mins before quenching the reaction with water (20mL) and basifying with $NaHCO_3$(aq). The product was extracted into DCM (2x15mL) and the combined DCM layers dried over $MgSO_4$, filtered and concentrated *in vacuo* to give ethyl 7-(4-chloromethylphenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate LCMS (ES^+) RT 3.97 minutes, 424 $(M+H)^+$. To a solution of this compound in DMF (1mL) was added 2-methylimidazole (13mg, 0.16mmol) and caesium carbonate (52mg, 0.16mmol) and the mixture heated at 80° for

3h. DMF was removed *in vacuo* and the residue purified by column chromatography (silica, 40-100% EtOAc in isohexane followed by 5% MeOH in DCM) and also mass directed hplc to give the title compound as a solid (3mg). δH (MeOH-d4) 7.47-7.27 (10H, m), 7.06 (1H, d, J 1.4Hz), 6.82 (1H, d, J 1.4Hz), 6.50 (1H, d, J 9.6Hz), 5.26 (2H, s), 4.00 (2H, q, J 7.1Hz), 2.28 (3H, s), 0.99 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.53 minutes, 470 $(M+H)^+$.

Example 111

Ethyl 7-(4-bromophenyl)-3-(2,4-difluorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To an oven dried flask was added in sequence 4-bromophenylboronic acid (4.2g, 20.88mmol), DCM (100mL), pyridine (1.7mL), Intermediate 14 (3.5g, 10.44mmol), copper(II) acetate (3.8g, 20.88mmol) and pyridine N-oxide (992mg). The reaction was stirred at room temperature for 7 days with the exclusion of moisture. A further equivalent each of $Cu(OAc)_2$, pyridine N-oxide and pyridine was added and reaction stirred for 20h. The reaction was then diluted with DCM (100mL), washed with 2M HCl(aq), $NaHCO_3$ (aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-3% THF in DCM) to give the title compound as an off-white solid (1.03g). LCMS (ES^+) RT 4.13 minutes, 489 $(M+H)^+$.

Example 112

Ethyl 3-(2,4-difluorophenyl)-7-[4-(4-methylpiperazin-1-yl)phenyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate hydrochloride

The title compound was prepared from the compound of Example 111 (1.0g, 2.04mmol) and N-methylpiperazine (230μL, 2.45mmol) following the analogous procedure described for the compound of Example 58. The crude product was purified by column chromatography (silica, 1% NH_3(aq) 10%MeOH 90% DCM) to give the product as a yellow solid (320mg). This solid was dissolved in DCM and treated with 4M HCl(aq). Solvent was

removed *in vacuo* and the residue re-dissolved in hot DCM. The solution was allowed to cool and the resultant solid collected by filtration to give the title compound as an off-white solid (310mg). δH (DMSO-d6) 7.66-7.52 (5H, m), 7.39-7.33 (3H, m), 6.67 (1H, d, J 9.6Hz), 4.10 (2H, q, J 3.1Hz), 3.50-3.10 (8H, m), 2.94 (3H, s), 1.19 (3H, q, J 3.1Hz). LCMS (ES^+) RT 2.57 minutes, 510 $(M+H)^+$.

Example 113

3-(2,4-Difluorophenyl)-7-[4-(4-methylpiperazin-1-yl)phenyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine

To a solution of the compound of Example 112 (310mg, 0.61mmol) in dioxane (35mL) was added 4M HCl(aq) (20mL) and the mixture heated at reflux for 18h. Reaction had not reached completion and so a few drops of concentratedHCl were added and reflux continued for 5h. The reaction was quenched with saturated Na_2CO_3(aq) and extracted with DCM (x3). The combined DCM extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product contained a small amount of residual ester starting material. The product was therefore dissolved in EtOH (15mL) and heated at reflux with NaOH (50mg) for 16h. Solvent was removed *in vacuo* and the residue partitioned between DCM and saturated Na_2CO_3(aq). The DCM layer was washed with Na_2CO_3(aq) (x3), dried (Na_2SO_4) and concentrated *in vacuo* to give the pure title compound as an off-white solid (280mg). δH (DMSO-d6) 8.10-7.95 (2H, m), 7.86 (1H, dt, J 9.5, 2.6Hz), 7.74-7.63 (4H, m), 7.55-7.52 (2H, m), 6.92 (1H, d, J 9.5Hz), 3.72-3.67 (8H, m), 2.67 (3H,s). LCMS (ES^+) RT 2.47 minutes, 438 $(M+H)^+$.

Example 114

1,4-Diphenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one

Intermediate 17 (230mg, 1.1mmol) copper(II) acetate (22mg, 0.11mmol), pyridine N-oxide (209mg, 3.3mmol), and phenyl boronic acid (344mg, 2.2mmol) were suspended in DCM (5mL) and treated with pyridine (0.33mL, 3.3mmol). The reaction was stirred at r.t. for eighteen hours, further copper(II) acetate (415mg, 2.08mmol) was added and the reaction stirred for a further four hours. The reaction mixture was diluted with DCM, washed with ammonium chloride solution, separated, dried and concentrated *in vacuo*. Chromatography (ethyl acetate-silica) gave the title compound. δH (DMSO-d6) 7.75 (1H, d, J 9.6Hz), 7.57-7.34 (11H, m), 6.20 (1H, d, J 9.6Hz), 5.66 (1H, dd, J 0.6, 3.1Hz). LCMS (ES^+) RT 3.278 minutes, $287(M+H)^+$.

Example 115

4-(4-Methoxyphenyl)-1-phenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one

The title compound was prepared from 4-methoxyphenylboronic acid and Intermediate 17 following the method described for the compound of Example 114. δH (DMSO-d6) 7.01 (1H, d, J 9.6Hz), 7.8-7.6 (6H, m), 7.49 (1H, d, J 8.9Hz), 7.27 (1H, d, J 8.9Hz), 6.42 (1H, d, J 9.6Hz), 5.91 (1H, d, J 2.8Hz), 4.01 (3H, s). LCMS (ES^+) RT 3.299 minutes, $317(M+H)^+$

Example 116

Ethyl 6-Oxo-3-phenyl-7-pyridin-3-ylmethyl-6,7-dihydro-thieno[2,3-*b*]pyridine-2-carboxylate

To a solution of Intermediate 4 (200 mg, 0.67 mmol) in DMF (5 mL) at 0° was added sodium hydride (60 mg, 1.5 mmol, 60 % dispersion in mineral oil) and the solution stirred for 5 minutes. 3-(Bromomethyl)-pyridine (202 mg, 0.8 mmol) was added and the reaction heated at 65° for 18 hours. The reaction was poured into saturated ammonium chloride solution and the aqueous phase extracted with EtOAc (x3). The organic phases were dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. Column chromatography (silica, 20 % THF in DCM) gave the title product as an off white solid (110 mg). δH

($CDCl_3$) 9.00 - 8.25 (2H, bm), 7.76 (1H, d, J 7.8 Hz), 7.40 – 7.35 (3H, m), 7.32 (1H, d, J 9.2 Hz), 7.26 – 7.18 (3H, m), 6.51 (1H, d, J 9.2 Hz), 5.33 (2H, s), 4.11 (2H, q, J 7.1 Hz), 1.09 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.25 minutes, 391 $(M+H)^+$

Example 117
Ethyl 7-(1-Benzyloxycarbonyl-piperidin-4-ylmethyl)-6-oxo-3-phenyl-6,7-dihydro-thieno[2,3-*b*]pyridine-2-carboxylate

To a solution of Intermediate 4 (1.0g, 3.35 mmol) in DMF (10mL) at 0° was added sodium hydride (160mg, 4.0 mmol, 60 % dispersion in mineral oil) and the solution stirred for 5 minutes. *N*-Benzyloxycarbonyl-4-bromomethylpiperidine (1g, 4 mmol) was added and the reaction heated at 65° for 18 hours. The reaction was poured into saturated ammonium chloride solution and the aqueous phase extracted with EtOAc (x3). The organic phases were dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. Column chromatography (silica, 0-15% EtOAc in DCM) gave the title product as an off white solid (410 mg). δH ($CDCl_3$) 7.40 - 7.36 (3H, m), 7.30 – 7.23 (8H, m), 6.42 (1H, d, J 9.6 Hz), 5.06 (2H, s), 4.28 – 3.80 (4H, bm), 4.13 (2H, q, J 7.0 Hz), 2.80 (2H, m), 2.26 (1H, m), 1.70 (2H, m), 1.42 (2H, m), 1.12 (3H, t, J 7.0 Hz). LCMS (ES^+) RT 4.24 minutes, 531 $(M+H)^+$

Example 118
Ethyl 6-Oxo-3-phenyl-7-piperidin-4-ylmethyl-6,7-dihydro-thieno[2,3-*b*]pyridine-2-carboxylate

The compound of Example 117 (400 mg) was dissolved in EtOH (20 mL) and 10 % palladium on carbon (40 mg) added. A hydrogen atmosphere (1 atmosphere) was applied and the reaction allowed to stir at ambient temperature for 18 hours. The reaction was filtered and the solvents removed *in vacuo* to give the title product as a white solid (210 mg). δH ($CDCl_3$) 7.50 - 7.45 (3H, m), 7.28 – 7.20 (3H, m), 6.42 (1H, d, J 9.6Hz), 4.12 (2H, q, J 7.1 Hz), 3.98 (2H, d, J 7.4Hz), 3.05 (2H, m), 2.55 (2H, m), 2.18 (1H, m), 1.60

(2H, m), 1.30 (2H, m), 1.11 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.43 minutes, 397 $(M+H)^+$

Example 119

Ethyl 7-(1-Methanesulfonyl-piperidin-4-ylmethyl)-6-oxo-3-phenyl-6,7-dihydro-thieno[2,3-*b*]pyridine-2-carboxylate

The compound of Example 118 (104 mg, 0.26 mmol) was dissolved in DCM (5 mL) and triethylamine (73 μL) followed by methanesulphonylchloride (40 μL, 0.28 mmol) added. The reaction was allowed to stir at ambient temperature for 18 hours. The reaction was diluted with brine and extracted with DCM (x3). The organic phases were washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). The reaction was filtered and the solvents removed *in vacuo* to give the title product as a white solid (120mg). δH ($CDCl_3$) 7.45 - 7.30 (3H, m), 7.27 - 7.10 (3H, m), 6.43 (1H, d, J 9.4 Hz), 4.12 (2H, q, J 7.1 Hz), 4.02 (2H, d, J 7.2 Hz), 3.75 (2H, m), 2.70 (3H, s), 2.61 (2H, m), 2.20 (1H, m), 1.82 (2H, m), 1.55 (2H, m), 1.12 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.55 minutes, 475 $(M+H)^+$

Example 120

Ethyl 7-(2-nitrophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Sodium hydride (440mg of a 60% suspension in mineral oil, 11mmol) was added portionwise to a suspension of Intermediate 4 (2.99g, 10mmol) in DMF (50mL) at r.t. 1-Fluoro-2-nitrobenzene (1.48mL, 15mmol) was added and the mixture heated at 80° for 4 days. The reaction was quenched with a few drops of water and the solvent removed *in vacuo*. Purification by column chromatography on silica (DCM to 5%MeOH in DCM then in 2%THF in DCM) gave the title compound (807mg, 19%) as a yellow solid. δH (DMSO-d6) 8.44 (1H, dd, J 1.3, 8.2Hz), 8.17-8.08 (2H, m), 8.03-7.98 (1H, m), 7.61-7.57 (4H, m), 7.53-7.50 (2H, m), 6.62 (1H, d, J 9.7Hz), 4.14 (2H, q, J 7.1Hz), 1.12 (3H, t, J, 7.1Hz).). LCMS (ES^+) RT 3.748 minutes, 421.0 $(M+H)^+$.

Example 121
Ethyl 7-(2-aminophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of the compound of Example 120 (455mg, 1.08mmol) and palladium on charcoal (10% Pd wt/wt, 90mg) in EtOH (20mL) was stirred under an atmosphere of hydrogen (balloon) for 45h. The catalyst was filtered off and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica (3% to 5%THF in DCM) gave the title compound as a pale yellow solid (257mg, 61%). δH (DMSO-d6) 7.59-7.52 (3H, m), 7.48-7.44 (3H, m), 7.33-7.28 (1H, m), 7.16 (1H, dd, J 1.5, 7.8Hz), 6.98 (1H, dd, J 1.2, 8.2Hz), 6.77-6.73 (1H, m), 6.59 (1H, d, J 9.6Hz), 5.33 (2H, br s), 4.12 (2H, q, J 7.1Hz), 1.12 (3H, t, J 7.1Hz).). LCMS (ES^+) RT 3.581 minutes, 391.0 $(M+H)^+$.

Example 122
Ethyl 7-(2-ethylaminophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Obtained from the compound of Example 120 by the method of Example 121 using longer reaction times. White solid. δH (DMSO-d6) 7.60-7.54 (3H, m), 7.50-7.45 (3H, m), 7.43-7.39 (1H, m), 7.18 (1H, dd, J 1.5, 7.7Hz), 6.93 (1H, d, J 7.7Hz), 6.79-6.75 (1H, m), 6.59 (1H, d, J 9.6Hz), 5.47 (1H, t, J 5.8Hz), 4.13 (2H, q, J 6.9Hz), 3.18 (2H, qn, J 6.7Hz), 1.13 (3H, t, J 7.0Hz), 1.11 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.947 minutes, 419.1 $(M+H)^+$.

Example 123
7-(2-Nitrophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

A mixture of the compound of Example 120 (150mg, 0.357mmol) and lithium hydroxide monohydrate (30mg, 0.714mmol) in dioxane (3mL) and water (3mL) was heated under reflux for 1.5h. The dioxane was removed *in vacuo*,

the aqueous residue acidified (2M HCl) and the precipitate filtered off and dried to give the title compound as a pale orange solid (112mg, 80%). δH (DMSO-d6) 13.06 (1H, br s), 8.29 (1H, dd, J 1.3, 8.2Hz), 8.02-7.93 (2H, m), 7.88-7.84 (1H, m), 7.46-7.35 (6H, m), 6.46 (1H, d, J 9.7Hz). LCMS (ES^+) RT 3.137 minutes, 393.0 $(M+H)^+$.

Example 124
7-(2-Nitrophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

A mixture of the compound of Example 123 (105mg, 0.268mmol) and 1,1'-carbonyldiimidazole (65mg, 0.40mmol) in DMF (3mL) was stirred at r.t. for 45min. Concentrated ammonia solution (1mL) was added and the mixture stirred overnight at r.t. Volatiles were removed *in vacuo*, the residue taken up in DCM, washed 2M HCl(aq), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography on silica (4%MeOH in DCM) gave the title compound as a yellow solid (42mg). δH (DMSO-d6) 8.28 (1H, dd, J 1.3, 8.2Hz), 7.99 (1H, dt, J 1.4, 7.8Hz), 7.92 (1H, dd, J 1.4, 7.8Hz), 7.87-7.82 (1H, m), 7.54-7.47 (3H, m), 7.46-7.37 (3H, m), 6.44 (1H, d, J 9.7Hz), 6.21 (2H, v br). LCMS (ES^+) RT 2.997 minutes, 392.0 $(M+H)^+$.

Example 125
Ethyl 7-(2-chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

tert-Butyl nitrite (0.145mL, 1.22mmol) was added to a suspension of copper (II) chloride (120mg, 0.894mmol) in acetonitrile (10mL) at 0°C. After 10min, a solution of the compound of Example 121 (317mg, 0.813mmol) in acetonitrile (5mL) was added. The mixture was stirred at 0° for 30min then warmed to r.t. The solvent was removed *in vacuo*, the residue dissolved in DCM, washed HCl (2M), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica (2% to 3% THF in DCM) gave the title compound as a yellow solid (163mg, 49%). δH (DMSO-d6) 7.91 (1H, ddd, J 1.7, 7.7Hz),

7.86-7.83 (1H, m), 7.78-7.70 (2H, m), 7.60-7.57 (4H, m), 7.53-7.49 (2H, m), 6.66 (1H, d, J 9.7Hz), 4.13 (2H, q, J 7.1Hz), 1.11 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.944 minutes, 410.0 $(M+H)^+$.

Example 126

7-(2-Chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

Obtained from the compound of Example 125 by the method of Example 123. Off-white solid. δH (DMSO-d6) 13.09 (1H, br s), 7.86-7.82 (1H, m), 7.78-7.76 (1H, m), 7.71-7.64 (2H, m), 7.52-7.41 (6H, m), 6.58 (1H, d, J, 9.7Hz). LCMS (ES^+) RT 3.247 minutes, 381.9 $(M+H)^+$.

Example 127

7-(2-Chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

A mixture of the compound of Example 126 (125mg, 0.328mmol) and 1,1'-carbonyldiimidazole (80mg, 0.49mmol) in DMF (3mL) was stirred at r.t. for 90min. Concentrated ammonia solution (0.5mL) was added and the mixture stirred for 1h. Volatiles were removed *in vacuo*. The residue was treated with 2M HCl(aq) and the resulting solid filtered off and dried. Purification by column chromatography on silica (3% MeOH in DCM) gave the title compound as a pale brown solid (105mg, 84%). δH (DMSO-d6) 7.91-7.89 (1H, m), 7.83-7.80 (1H, m), 7.76-7.69 (2H, m), 7.66-7.59 (3H, m), 7.56-7.53 (2H, m), 7.51 (1H, d, J 9.7Hz), 6.62 (1H, d, J 9.6Hz), 6.2 (2H, br s). LCMS (ES^+) RT 3.120 minutes, 380.8 $(M+H)^+$.

Example 128

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbothioamide

Hydrogen sulphide was bubbled through a solution of the compound of Example 77 (539mg, 1.64mmol) in pyridine (10mL) and triethylamine (0.5mL) for 30 minutes. The reaction was left to stand for 60h at r.t. and then nitrogen

bubbled through the mixture to ensure the solution was purged of H_2S. The solution was diluted with DCM and washed with water (x2), 2M HCl(aq) (x2) and brine. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was recrystallised from DCM-hexane to give the title compound as a solid (327mg, 40%). δH (DMSO-d6) 9.70 (1H, s), 7.70-7.47 (9H, m), 7.45 (2H, m), 7.38 (1H, d J 9.6Hz), 6.52 (1H, d, J 9.6Hz). LCMS (ES^+) RT 3.33 minutes, 385 $(M+Na)^+$, 363 $(M+H)^+$.

Example 129

7-(2-chlorophenyl)-6-Oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbothioamide

To a mixture of Lawesson's reagent (26.3mg, 0.065 mmol) and the compound of Example 127 (50mg, 0.13mmol) was added toluene (10mL) and the reaction heated at 110° for 1h. A further portion of Lawesson's reagent (52.6mg, 0.13mmol) was added and reaction heated for 6.5h. The reaction was diluted with DCM, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 5-10%EtOAc in DCM) to give the title compound as a yellow solid (10mg, 20%). δH (MeOH-d4) 7.67 (1H, m), 7.58-7.46 (7H, m), 7.40 (3H, m), 6.48 (1H, d, J 9.6Hz). LCMS (ES^+) RT 3.41 minutes, 397 $(M+H)^+$.

The following assays and animal models can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each assay an IC50 value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition.

Preparation of activated human p38α for inhibitor assays.

Purification of human p38α

Human p38α, incorporating an N-terminal (His)6 tag, was expressed in baculovirus-infected High-Five™ cells (Invitrogen) according to the manufacturers instructions. The cells were harvested 72h post-infection and lysed in phosphate buffered saline (PBS) containing 1% (w/v) β-octylglucoside and Complete, EDTA-free™ protease inhibitors (Roche Molecular Biochemicals). The lysate was centrifuged at 35000xg for 30min at 4oC and the supernatant applied to a NiNTA™ column (Qiagen). Bound protein was eluted by 150mM imidazole in PBS (after a wash with 15mM imidazole in PBS) and directly applied to a HiTrap Q™ column (AP Biotech). Bound protein was eluted using a 20 column volume, 0 to 1M NaCl gradient. Fractions containing (His)6-p38 were aliquotted and stored at –70º prior to their activation.

<u>Preparation of GST-MKK6EE-containing lysates</u>

E. coli (BL21 pLysS) expressing the constituitively activated form of human MKK6 fused with an N-terminal glutathione–S-transferase tag (GST-MKK6EE) were harvested by centrifugation and frozen at –70º. Cells were lysed by resuspension in 1/10th the culture volume of PBS containing Complete, EDTA-free™ protease inhibitors followed by sonication on ice for 4x15 sec. Cell debris was removed by centrifugation at 35,000xg and the resultant supernatant stored in aliquots at –70º.

<u>Activation of (His)6-p38</u>

0.45mL of purified (His)6-p38 was incubated with 50μL of the GST-MKK6EE-containing lysate for 30min at 23º in the presence of 1mM β-glycerophosphate, 10mM $MgCl_2$ and 9mM ATP. The extent of activation was monitored by mass spectrometric detection of the doubly-phosphorylated form of (His)6-p38, which routinely comprised greater than 90% of the final (His)6-p38 preparation. The activated (His)6-p38 was then diluted x10 in PBS and repurified using the method described above. The concentration of

purified, activated (His)6-p38 was measured by UV absorbance at 280nm using A280,0.1%=1.2 and the preparation stored in aliquots at –70º prior to its use in inhibitor assays.

p38 Inhibition Assays

Inhibition of phosphorylation of biotinylated myelin basic protein (MBP)

The inhibition of p38 catalysed phosphorylation of biotinylated MBP is measured using a DELFIA based format. The assay was performed in a buffer comprising, 20mM HEPES (pH 7.4), 5mM $MgCl_2$ and 3mM DTT. For a typical IC50 determination, biotinylated MBP (2.5μM) was incubated at room temperature in a streptavidin-coated microtitre plate together with activated gst-p38 (10nM) and ATP (1μM) in the presence of a range of inhibitor concentrations (final concentration of DMSO is 2 percent). After fifteen minutes the reaction was terminated by the addition of EDTA (75mM). The microtitre plate was then washed with Tris buffered saline (TBS), prior to the addition of 100μl of anti-phospho MBP antibody (mouse) together with europium-labeled anti-mouse IgG antibody. After one hour at room temperature the plate was again washed in TBS followed by the addition of Enhancement solution (PerkinElmer Wallac). Fluorescence measurements were performed after a further fifteen minutes at room temperature.

IC50 values are determined from the plot of Log_{10} inhibitor concentration (x-axis) versus percentage inhibition of the fluorescence generated by a control sample in the absence of inhibitor (y-axis).

Purification of human Peripheral Bood Mononuclear Cells

Peripheral blood mononuclear cells (PBMC) were isolated from normal healthy volunteers. Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), diluted 1 in 4 in RPMI 1640 (Gibco, UK) and centrifuged at 400g for 35 min over a Ficoll-paque gradient

(Amersham-Pharmacia Biotech, UK). Cells at the interface were removed and washed once followed by a low speed spin (250g) to remove platelets. Cells were then resuspended in DMEM containing 10% FCS, penicillin 100 units ml^{-1}, streptomycin 50µg ml^{-1} and glutamine 2mM (Gibco, UK).

Inhibitor dilutions

Inhibitor stocks (20mM) were kept as a frozen solution (-20°C) in DMSO. Serial dilutions of inhibitors were performed in DMSO as 250-times concentrated stocks. Inhibitors were diluted 1 in 250 into tissue culture media, prewarmed to 37°C and transferred to plates containing PBMC. PBMC and inhibitors were incubated together for 30 mins prior to addition of LPS. Inhibitors used in whole blood assays were prepared according to a different regime. Using the same stock solution serial dilutions of inhibitors were performed in DMSO. Inhibitors were then diluted 1 in 500 straight into whole blood in a volume of 1µL. Inhibitor was incubated with whole blood for 30 mins prior to the addition of LPS.

LPS stimulation of PBMC

PBMC were resuspended at a density of $2x10^5$ cells/well in flat bottomed 96 well tissue culture treated plates. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final concentration of 1µg ml^{-1}) and incubated at 37°C in 5%CO_2/95% air for 18 hours. TNF-α levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

LPS stimulation of whole blood

Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), and 500µl of blood aliquoted into each well of a 24 well tissue culture treated plate. After the addition of inhibitor cells were

stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final concentration of 1µg ml^{-1}) and incubated at 37°C without CO_2 for 18 hours. TNF-α levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

Rat LPS induced TNF release

Male Lewis rats (180-200g) are anaesthetised with Isofluor and injected i.v. with LPS* in a volume of 0.5ml sterile saline. After 90minutes blood is collected into EDTA tubes for preparation of plasma samples. Plasma is stored at –70°C prior to assay for TNFα by commercial ELISA.

Rat CIA

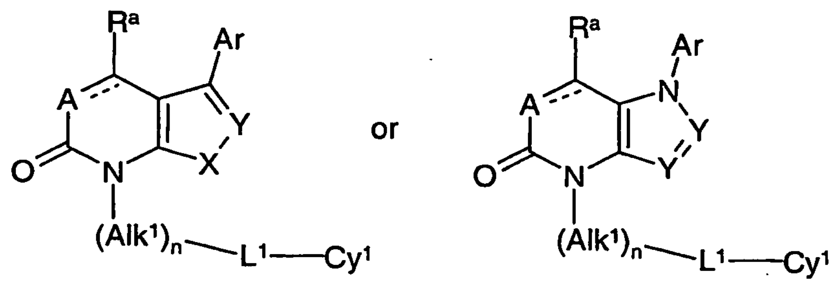
Female Lewis rats (180-200g) are anaesthetised with Isofluor and immunised i.d. at the base of the tail with 2x100µl of emulsion containing 4mg/ml bovine collagen II in 0.01M acetic acid and Freund's Incomplete Adjuvant at a ratio of 1:1.

A polyarthritis develops with onset from about 13 days post sensitisation. The disease is mainly confined to the ankles and is quantified by plethysmometry. Results are expressed as change in paw volume over time.

In the p38 inhibitor assay compounds of the invention have IC_{50} values of around 30µM and below. The more active compounds have IC_{50} values of around 500nM and below. The compounds of the invention are clearly potent inhibitors of p38 kinase, especially p38α kinase.

CLAIMS

1. A compound of formula (1a) or (1b):



(1a) (1b)

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a –N(R^b)-, –C(R^b)= or –C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

X is an –O- or –S- atom or –NH- group or substituted N atom;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

for use in the prophylaxis or treatment of a p38 kinase mediated disease or disorder.

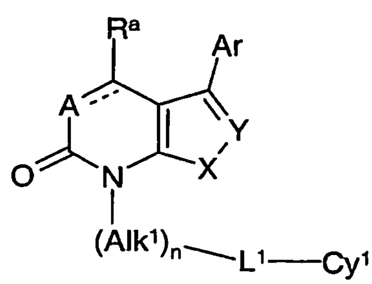
2. A compound according to claim 1 for use in the prophylaxis or treatment of a cytokine mediated disease or disorder.

3. A compound according to claim 1 for use in the prophylaxis or treatment of an immune or inflammatory disorder.

4. A compound according to claim 1 for use in the prophylaxis or treatment of rheumatoid arthritis.

5. The use of a compound according to Claim 1 for the manufacture of a medicament for the prophylaxis or treatment of a disease or disorder according to Claims 1 to 5.

6. A compound of formula (1a):



(1a)

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a –N(R^b)-, –C(R^b)= or –C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

X is an –O- or –S- atom or –NH- group or substituted N atom;

Y is a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

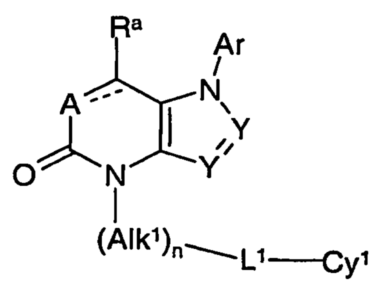
Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

7. A compound according to Claim 6 in which Cy^1 is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

8. A compound according to Claim 6 or Claim 7 in which X is an –O- or –S- atom.

9. A compound of formula (1b):



(1b)

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a $-N(R^b)-$, $-C(R^b)=$ or $-C(R^b)(R^c)-$ group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

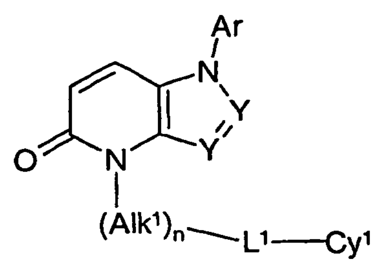
Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

with the proviso that when the compound of formula (1b) is a compound of formula (1c):



(1c)

in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH{=}CH-$, $-CH_2CH{=}CCl-$, $-CH_2CC-$ or $-CF_2-$ chain then Cy^1 is other than a hydrogen atom; or in which

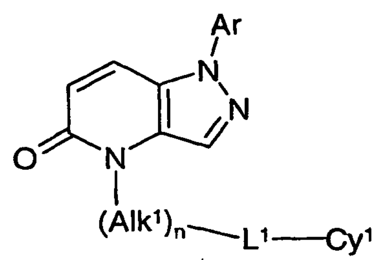
each Y is a N atom or a CH group, Ar is a 3-chloro-5-trifluoromethylpyridin-2-yl group, L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ chain then Cy^1 is other than a hydrogen atom; or in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is

a covalent bond and n is zero then Cy^1 is other than a cyclopropyl group; or in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl, 2-chloro-6-fluoro-4-trifluoromethylphenyl or 3-chloro-5-trifluoromethylpyridin-2-yl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a hydrogen atom;

and with the further proviso that when the compound of formula (1b) is a compound of formula (1d):



(1d)

in which:

L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$ chain then Ar is other than a 3-methyl-5-trifluoromethylpyridin-2-yl, 5-trifluoromethylpyridin-2-yl, 3-trifluoromethylpyridin-2-yl, 3,5-difluoropyridin-2-yl, 3,5-dichloropyridin-2-yl or 2-chloro-4-trifluoromethylphenyl group; and the salts, solvates, hydrates and N-oxides thereof;

10. A compound according to any one of Claims 6 to 9 in which Cy^1 is an optionally substituted cycloaliphatic, aromatic or heteroaromatic group.

11. A compound according to Claim 10 in which Cy^1 is an optionally substituted phenyl group.

12. A compound according to any one of Claims 6 to 11 in which Ar is an optionally substituted phenyl or monocyclic five- or six-membered heteroaromatic group.

13. A compound according to Claim 12 in which Ar is an optionally substituted phenyl group.

14. A compound according to any one of Claims 6 to 13 in which R^a is a hydrogen atom or methyl group.

15. A compound according to any one of Claims 6 to 14 in which L^1 is a covalent bond or an –O- or –S- atom or an $–N(R^2)-$ [where R^2 is a hydrogen atom or a straight or branched alkyl group], -C(O)-, -C(S)-, -S(O)- or $–S(O)_2-$ group.

16. A compound according to Claim 15 in which L^1 is a covalent bond.

17. A compound according to any one of Claims 6 to 16 in which n is zero.

18. A compound according to any one of Claims 6 to 17 in which each Y is a CH group or a substituted C atom.

19. A compound according to any one of claims 6 to 18 in which the dashed line represents a bond and A is a $–C(R^b)=$ group.

20. A compound according to Claim 19 in which R^b is a hydrogen atom.

21. A compound which is:
Ethyl 6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;
Ethyl 7-cyclopropylmethyl-6-oxo-3-phenyl -6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;
Ethyl 6-oxo-3-phenyl-7-(3-thienyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(4-fluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(2-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 6-oxo-7-phenyl-3-(4-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(3-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

6-Oxo-3,7-diphenyl-*N*-(2-piperidinoethyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide;

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile;

3,7-Diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one;

Ethyl 3-(2,4-difluorophenyl)-7-[4-(4-methylpiperazin-1-yl)phenyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

1,4-Diphenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one;

Ethyl 7-(2-chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

and the salts, solvates, hydrates and N-oxides thereof.

22. A pharmaceutical composition comprising a compound according to any one of Claims 6 to 21 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/04680

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04 C07D471/04 A61K31/4365 A61K31/437 A61P19/02 A61P29/00 A61P37/02 //(C07D495/04,333:00,221:00), (C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64400 A (BEMIS GUY; VERTEX PHARMA (US); COCHRAN JOHN (US); SALITURO FRANCES) 16 December 1999 (1999-12-16) page 1, line 2 - line 10; claims 1-19,21-24,31,32 ---	1-22
A	WO 01 64679 A (SMITHKLINE BEECHAM CORP; ADAMS JERRY L (US); BOEHM JEFFREY C (US);) 7 September 2001 (2001-09-07) claims 1,18-21,28-31,38-41,51-53 ---	1-6,9,22
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2003	06/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 623 598 A (OTSUKA PHARMA CO LTD) 9 November 1994 (1994-11-09) claims 1,4-6	1-5,22
A	EP 0 090 275 A (LEPETIT SPA) 5 October 1983 (1983-10-05) page 6, line 6 - line 20; claims 1,6-8	1,3,6,7, 22
A	JP 09 059276 A (KUMIAI CHEM IND CO LTD; IHARA CHEM IND CO LTD) 4 March 1997 (1997-03-04) cited in the application page (5), compounds no. 24, 32 and 40; page (6), compounds no. 58, 66 and 75; page (7), compounds no. 91, 100, 108 and 116; page (8), compounds no. 128 and 136; page (9), compounds no. 140, 148 and 156	9
A	-& PATENT ABSTRACTS OF JAPAN vol. 1997, no. 07, 31 July 1997 (1997-07-31) & JP 09 059276 A , 4 March 1997 (1997-03-04) cited in the application abstract	9

INTERNATIONAL SEARCH REPORT

PCT/GB 02/04680

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			US	4530927	A	23-07-1985
			ZA	8301738	A	25-01-1984
JP 09059276	A	04-03-1997	NONE			

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(10) International Publication Number
WO 03/033502 A1

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(30) Priority Data:
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(72) Inventors; and
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(74) Common Representative: **CELLTECH R & D LIMITED**; Patents Department, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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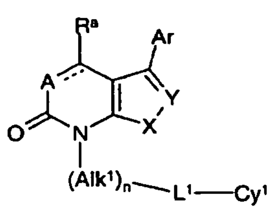
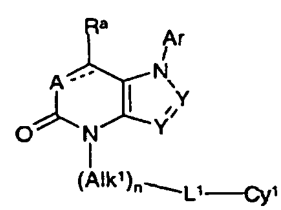
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BICYCLIC OXOPYRIDINE AND OXOPYRIMIDINE DERIVATIVES



(1a)



(1b)

(57) Abstract: Compounds of formulae (1 a) and (1 b) are described: in which the dashed line represents an optional bond; A is a -N= atom or a -N(R^b)-, -C(R^b)= or -C(R^b)(R^C)- group; R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C^{1-6}alkyl group; X is an -O- or -S- atom or -NH- group or substituted N atom; each Y is independently a N atom or CH group or substituted C atom; n is zero or the integer 1; Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain L^1 is a covalent bond or a linker atom or group; Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group; Ar is an optionally substituted aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof; The compounds are potent inhibitors of p38 kinase and are use in the prophylaxis or treatment of p38 kinase mediated diseases or disorders, such as rheumatoid arthritis.

WO 03/033502 A1

BICYCLIC OXOPYRIDINE AND OXOPYRIMIDINE DERIVATIVES

This invention relates to a series of 5-6 fused ring bicyclic heteroaromatic derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

Immune and inflammatory responses involve a variety of cell types with control and co-ordination of the various interactions occurring *via* both cell-cell contacts (e.g integrin interactions with their receptors) and by way of intercellular signalling molecules. A large number of different signalling molecules are involved including cytokines, lymphocytes, chemokines and growth factors.

Cells respond to such intercellular signalling molecules by means of intracellular signalling mechanisms that include protein kinases, phosphatases and phospholipases. There are five classes of protein kinase of which the major ones are the tyrosine kinases and the serine/threonine kinases [Hunter, T., Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T. and Sefton, B.M.; eds. Vol. 200, Academic Press; San Diego, 1991].

One sub-class of serine/threonine kinases is the mitogen activating protein (MAP) kinases of which there are at least three families which differ in the sequence and size of the activation loop [Adams, J. L. *et al*, Progress in Medicinal Chemistry p. 1-60, King, F. D. and Oxford, A. W.; eds. vol 38, Elsevier Science, 2001]: the extracellular regulated kinases (ERKs), the c-Jun NH_2 terminal kinases or stress activated kinases (JNKs or SAP kinases) and the p38 kinases which have a threonine-glycine-tyrosine (TGY) activation motif. Both the JNKs and p38 MAP kinases are primarily activated by stress stimuli including, but not limited to, proinflammatory cytokines e.g.

tumour necrosis factor (TNF) and interleukin-1 (IL-1), ultraviolet light, endotoxin and chemical or osmotic shock.

Four isoforms of p38 have been described (p38α/β/γ/δ). The human p38α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially termed CSAID binding protein-1 (CSBP-1) and CSBP-2 [Lee, J. C. *et al*, Nature (London) 1994, 372, 739-46]. CSBP-2 is now widely referred to as p38α and differs from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons that are conserved in both mouse and human [McDonnell, P. C. et al, Genomics 1995, 29, 301-2]. CSBP-1 and p38α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38β which has 70% identity with p38α. A second form of p38β termed p38β2 is also known and of the two this is believed to be the major form. p38α and p38β2 are expressed in many different tissues. However in monocytes and macrophages p38α is the predominant kinase activity [Lee, J. C., *ibid*; Jing, Y. *et al*, J. Biol. Chem. 1996, 271, 10531-34; Hale, K. K. *et al*, J. Immun. 1999, 162, 4246-52]. p38γ and p38δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have ~63% and ~61% homology to p38α respectively. p38γ is predominantly expressed in skeletal muscle whilst p38δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y. N. *et al* FEBS Lett., 1995, 364,

7095-8012]. This dual phosphorylation is effected by MKK6 and under certain conditions the related enzyme MKK3 (see Figure 1) [Enslen, H. *et al* J. Biol. Chem., 1998, 273, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.

Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF-β-activated kinase) are some of the enzymes identified as upstream activators of for MAPKKs. MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H. Cell, 1998, 95, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor-β (TGF-β). TNF-stimulated activation of p38 is believed to be mediated by the recruitment of TRAF2 [TNF receptor associated factor] and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and others substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1, IL-6, IFN-g and IL-10 is also partially inhibited [Kotlyarov, A. *et al* Nature Cell Biol. 1999, 1, 94-7]. Further, MAPKAP K2 from embryonic stem cells from p38α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. *et al*, J. Exp. Med. 2000, 191, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low µM range [Lee, J. C. *et al*, Int. J. Immunopharm. 1988, 10, 835] and exhibit activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J. C. et al, Annals N. Y. Acad. Sci. 1993, 696, 149]. In addition these small molecule inhibitors are known to also decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA2, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P. Trends Cell Biol. 1997, 7, 353-61].

A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and

other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resporption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS related complex.

Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition IL-1 has been linked to diabetes and pancreatic β cells [Dinarello, C. A. J. Clinical Immunology, 1985, 5, 287-97].

IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF and LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis which may contribute to increased adhesion of neutrophils to vascular endothelial cells. Many diseases are characterised by massive neutrophil infiltration. Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysozomal enzyme release and respiratory burst from neutrophils.

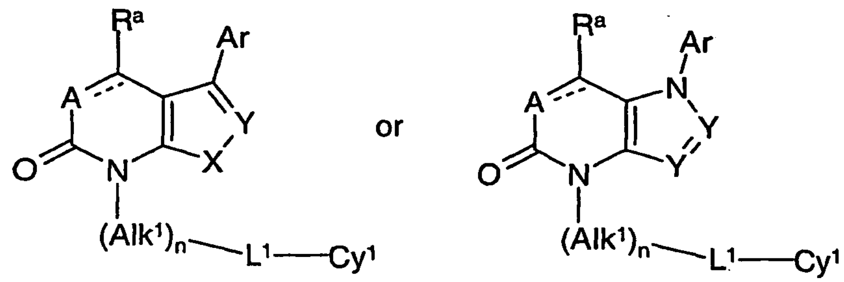
The central role of IL-1 and TNF together with other leukocyte derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin) make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger, *et al*, J. Pharm. Exp. Ther. 1996, 279, 1453-61; Griswold, *et al*, Pharmacol. Comm., 1996, 7, 323-29].

Japanese patent application No. JP09059276 describes a series of pyrazalopyridinones and analogs with utility as herbicides.

We have now found a group of compounds which are potent and selective inhibitors of p38 kinase (p38α, β, δ and γ) and the isoforms and splice variants thereof, especially p38α, p38β and p38β2. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

Thus according to one aspect of the invention we provide a compound of formula (1a) or (1b):



(1a) (1b)

wherein:

the dashed line represents an optional bond;

A is a -N= atom or a -N(R^b)-, -C(R^b)= or -C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

X is an -O- or -S- atom or -NH- group or substituted N atom;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

for the manufacture of a medicament for the prophylaxis or treatment of a p38 kinase mediated disease or disorder.

This invention also relates to a compound of formula (1a) or (1b) for use in the prophylaxis or treatment of a p38 kinase mediated disease or disorder in a mammal in need thereof.

This invention also relates to a compound of formula (1a) or (1b) for use in the prophylaxis or treatment of a cytokine mediated disease or disorder in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-6 in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof.

This invention more specifically relates to the administration to a mammal of an effective amount of a p38 kinase or cytokine, specifically IL-1, IL-6, IL-8 or TNF, inhibitor of formula (1a) or (1b).

Compounds according to the invention are potent and selective inhibitors of p38 kinases, including all isoforms and splice variants thereof. More specifically the compounds of the invention are inhibitors of p38α, p38β and p38β2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds of formula (1) are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8 include without limitation autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs, host disease or psoriasis.

The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis.

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastic melanoma and multiple myeloma.

Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury.

Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

In addition, p38 inhibitors of this invention also exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2) and are therefore of use in therapy. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly additional p38 mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

Thus TNF mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoiosis, bone resportion disease, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to

infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, viral infections such as HIV, CMV, influenza and herpes; and vetinary viral infections, such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Compounds of the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the TNF inhibiting compounds of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses such as Herpes Zoster and Herpes Simplex.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, diabetes, pancreatic β-cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis, inflammatory bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The increased IL-8 production associated with each of these diseases is responsible for the chemotaxis of neutrophils into

inflammatory sites. This is due to the unique property of IL-8 (in comparison to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in neutrophil infiltration.

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al*, Clin. Infec. Dis., 1997, 26, 840; Grunberg *et al*, Am. J. Crit. Care Med. 1997, 155, 1362; Zhu *et al*, J. Clin. Invest. 1996, 97, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al*, J. Clin. Invest. 1995, 96, 549]. Therefore, p38 inhibitors of the invention may be used for the treatment or prophylaxis of the common cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus or adenovirus infection.

For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine mediated disease the compounds according to the invention may be administered to a human or mammal as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1a) or (1b) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (1a) or (1b) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active

ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1a) or (1b) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds for use according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively the compounds for use according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for

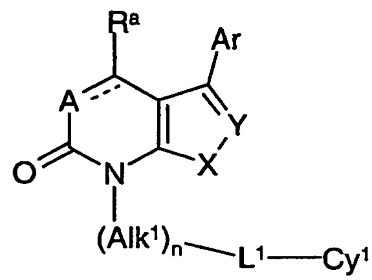
example mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds for use according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH adjusted sterile saline, either with or without a preservative such as bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds for use according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include for example cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

Particular compounds of formula (1a) and formula (1b) form a further aspect of the invention. Thus we provide a compound of formula (1a):



(1a)

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a $-N(R^b)-$, $-C(R^b)=$ or $-C(R^b)(R^c)-$ group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

X is an –O- or –S- atom or –NH- group or substituted N atom;

Y is a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

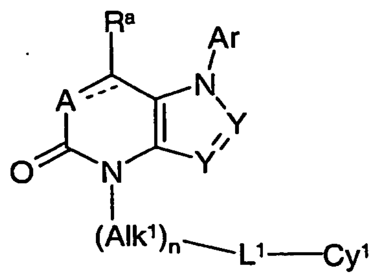
Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

Particular compounds of formula (1a) in which Cy^1 is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group form a further aspect of the invention.

In another particular aspect of the invention and we provide a compound of formula (1b):



(1b)

wherein:

the dashed line represents an optional bond;

A is a $-N=$ atom or a $-N(R^b)-$, $-C(R^b)=$ or $-C(R^b)(R^c)-$ group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

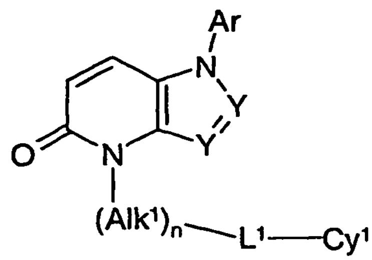
L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

with the proviso that when the compound of formula (1b) is a compound of formula (1c):



(1c)

in which

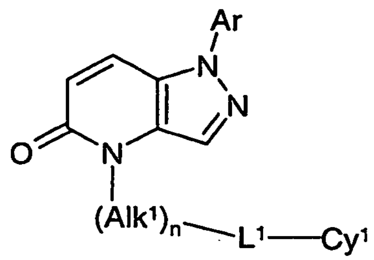
each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH{=}CH-$, $-CH_2CH{=}CCl-$, $-CH_2CC-$ or $-CF_2-$ chain then Cy^1 is other than a hydrogen atom; or in which

each Y is a N atom or a CH group, Ar is a 3-chloro-5-trifluoromethylpyridin-2-yl group, L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ chain then Cy^1 is other than a hydrogen atom; or in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a cyclopropyl group; or in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl, 2-chloro-6-fluoro-4-trifluoromethylphenyl or 3-chloro-5-trifluoromethylpyridin-2-yl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a hydrogen atom;

and with the further proviso that when the compound of formula (1b) is a compound of formula (1d):

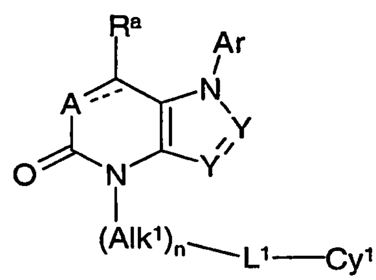


(1d)

in which:

L^1 is a covalent bond, n is the integer 1 and Alk^1 is a $-CH_2$- chain then Ar is other than a 3-methyl-5-trifluoromethylpyridin-2-yl, 5-trifluoromethylpyridin-2-yl, 3-trifluoromethylpyridin-2-yl, 3,5-difluoropyridin-2-yl, 3,5-dichloropyridin-2-yl or 2-chloro-4-trifluoromethylphenyl group.

Particular compounds of formula (1b) form a further aspect of the invention and we therefore provide a compound of formula and (1b'):



(1b')

wherein:

the dashed line represents an optional bond;

A is a –N= atom or a $-N(R^b)$-, $-C(R^b)$= or $-C(R^b)(R^c)$- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6}alkyl group;

each Y is independently a N atom or CH group or substituted C atom;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

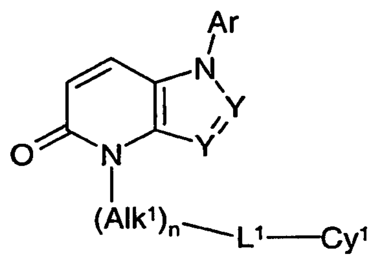
L^1 is a covalent bond or a linker atom or group;

Cy^1 an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

with the proviso that when the compound of formula (1b") is a compound of formula (1c):



(1c)

in which

each Y is a N atom or a CH group, Ar is a 2,6-dichloro-4-trifluoromethylphenyl or 2-chloro-6-fluoro-4-trifluoromethylphenyl group, L^1 is a covalent bond and n is zero then Cy^1 is other than a cyclopropyl group.

It will be appreciated that in the following detailed description of the invention all references to formula (1b) are also references to formulae (1b') unless specifically stated otherwise.

It will be further appreciated that compounds of formulae (1a) and (1b) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formulae (1a) and (1b) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formulae (1a) and (1b) may exist as tautomers, for example keto ($CH_2C=O$)-enol ($CH=CHOH$) tautomers. Formulae (1a) and (1b) and the

formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

The following general terms as used herein have the stated meaning unless specifically described otherwise.

As used herein the term "alkyl" whether present as a group or part of a group includes straight or branched C_{1-6}alkyl groups, for example C_{1-4}alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl or t-butyl groups. Similarly, the terms "alkenyl" or "alkynyl" are intended to mean straight or branched C_{2-6}alkenyl or C_{2-6}alkynyl groups such as C_{2-4}alkenyl or C_{2-4}alkynyl groups. Optional substituents which may be present on these groups include those optional substituents mentioned hereinafter in relation to Alk^1 when Alk^1 is an optionally substituted aliphatic chain.

The term halogen is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include those alkyl groups just mentioned sustituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CH_2F$ and $-CH_2Cl$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-6}alkoxy e.g. C_{1-4}alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ and $-OCH_2Cl$ groups.

As used herein the term "alkylthio" is intended to include straight or branched C_{1-6}alkylthio, e.g. C_{1-4}alkylthio such as methylthio or ethylthio.

As used herein the term "alkylamino or dialkylamino" is intended to include the groups $-NHR^1$ and $-N(R^1)_2$ [where R^1 is an optionally substituted straight or branched alkyl group]. Where two R^1 groups are present these may be the same or different. In addition where two R^1 groups are present these may be joined together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl group which may contain a further heteroatom or heteroatom containing group such as an –O- or -S- atom or –$N(R^1)$- group. Particular examples of such optionally substituted heterocycloalkyl groups include optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and N'-C_{1-6}alkyl-piperazinyl groups. The optional substituents which may be present on such heterocycloalkyl groups include those optional substituents as described hereinafter in relation to aliphatic chains.

When Alk^1 is present in compounds of formulae (1a) and (1b) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10}aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ chains.

Heteroaliphatic chains represented by Alk^1 in the compounds of formulae (1a) and (1b) include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-L^2CH_2-$, $-CH_2L^2-$, $-L^2CH(CH_3)-$, $-CH(CH_3)L^2-$, $-CH_2L^2CH_2-$, $-L^2CH_2CH_2-$, $-L^2CH_2CH(CH_3)-$, $-CH(CH_3)CH_2L^2-$, $-CH_2CH_2L^2-$, $-CH_2L^2CH_2CH_2-$, $-CH_2L^2CH_2CH_2L^2-$, $-(CH_2)_2L^2CH_2-$, $-(CH_2)_3L^2CH_2-$, $-L^2(CH_2)_2CH_2-$, $-L^2CH_2CHCH-$, $-CHCHCH_2L^2-$ and $-(CH_2)_2L^2CH_2CH_2-$ chains.

When L^2 is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include –O- or -S- atoms or –C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^2)-$ [where R^2 is a hydrogen atom or a straight or branched alkyl group], $-N(R^2)O-$, $-N(R^2)N-$, $-CON(R^2)-$, $-OC(O)N(R^2)-$, $-CSN(R^2)-$, $-N(R^2)CO-$, $-N(R^2)C(O)O-$, $-N(R^2)CS-$, $-S(O)_2N(R^2)-$, $-N(R^2)S(O)_2-$, $-N(R^2)CON(R^2)-$, $-N(R^2)CSN(R^2)-$ or $-N(R^2)SO_2N(R^2)-$ groups. Where L^2 contains two R^2 groups these may be the same or different.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, $-CO_2H$, $-CO_2R^4$ [where R^4 is an optionally substituted straight or branched C_{1-6}alkyl group], e.g. $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, $-CONHR^4$, e.g. $-CONHCH_3$, $-CON(R^4)_2$, e.g. $-CON(CH_3)_2$, $-COR^4$, e.g. $-COCH_3$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol (-SH), $-S(O)R^4$, e.g. –

$S(O)CH_3$, $-S(O)_2R^4$, e.g. $-S(O)_2CH_3$, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino, $-NHR^4$, e.g. $-NHCH_3$ or $-N(R^4)_2$, e.g. $-N(CH_3)_2$ groups. Where two R^4 groups are present in any of the above substituents these may be the same or different.

In addition when two R^4 alkyl groups are present in any of the optional substituents just described these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from –O-, -S-, $-N(R^4)-$, -C(O)- or –C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When L^1 is present in compounds of formulae (1a) and (1b) as a linker atom or group it may be any such atom or group as hereinbefore described in relation to L^2 linker atoms and groups.

Optionally substituted cycloaliphatic groups represented by the group Cy^1 in compounds of the invention include optionally substituted C_{3-10}cycloaliphatic groups. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl or C_{3-10}cycloalkenyl, e.g C_{3-7}cycloalkenyl groups.

Optionally substituted heterocycloaliphatic group represented by the group Cy^1 include optionally substituted C_{3-10}heterocycloaliphatic group. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7}heterocycloalkyl or C_{3-10}heterocycloalkenyl, e.g. C_{3-7}heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom containing groups L^4 in place of or in addition to the ring carbon atoms where L^4 is an atom or group as previously defined for L^2.

Optionally substituted polycycloaliphatic groups represented by the group Cy^1 include optionally substituted C_{7-10}bi-or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group Cy^1 include optionally substituted C_{7-10}bi- or tricycloalkyl or C_{7-10}bi- or tri-cycloalkenyl groups containing one, two, three, four or more L^4 atoms or groups in place of or in addition to the ring carbon atoms.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group Cy^1 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, 5,6-dihydro-2(1H)-pyrazinone, tetrahydropyrimidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, 1,3,5-oxadiazinyl, dihydroisothiazolyl, dihydroisothiazole 1,1-dioxide , e.g. 2,3-dihydroisothiazole 1,1-dioxide, dihydropyrazinyl and tetrahydropyrazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups

represented by the group Cy^1 include one, two, three or more substituents selected from halogen atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, eg. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthiol, e.g. methylthiol or ethylthiol, carbonyl (=O), thiocarbonyl (=S), imino ($=NR^{4a}$) [where R^{4a} is an $-OH$ group or a C_{1-6}alkyl group], or $-(Alk^3)_vR^5$ groups in which Alk^3 is a straight or branched C_{1-3}alkylene chain, v is zero or the integer 1 and R^5 is a C_{3-8}cycloalkyl, $-OH$, $-SH$, $-N(R^6)(R^7)$ [in which R^6 and R^7 is each independently selected from a hydrogen atom or an optionally substituted alkyl or C_{3-8}cycloalkyl group], $-OR^6$, $-SR^6$, $-CN$, $-NO_2$, $-CO_2R^6$, $-SOR^6$, $-SO_2R^6$, $-SO_3R^6$, $-OCO_2R^6$, $-C(O)R^6$, $-OC(O)R^6$, $-C(S)R^6$, $-C(O)N(R^6)(R^7)$, $-OC(O)N(R^6)(R^7)$, $-N(R^6)C(O)R^7$, $-C(S)N(R^6)(R^7)$, $-N(R^6)C(S)R^7$, $-SO_2N(R^6)(R^7)$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)N(R^7)(R^8)$ [where R^8 is as defined for R^6], $-N(R^6)C(S)N(R^7)(R^8)$, $-N(R^6)SO_2N(R^7)(R^8)$ or an optionally substituted aromatic or heteroaromatic group.

Particular examples of Alk^3 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$ chains.

When R^5, R^6, R^7 and/or R^8 is present as a C_{3-8}cycloalkyl groups it may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-6}alkoxy, e.g. methoxy, ethoxy or *i*-propoxy groups.

When the groups R^6 and R^7 or R^7 and R^8 are both alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a

heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from –O-, -S-, –N(R^7)-, -C(O)- or –C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When R^5 is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter in relation to Cy^1.

Additionally, when the group Cy^1 is a heterocycloaliphatic or heteropolycycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^5)_p(Alk^4)_qR^9$ in which L^5 is a –C(O)-, -C(O)O-, -C(S)-, -S(O)$_2$-, -CON(R^6)- or –SO$_2$N(R^6)-; p is zero or the integer 1; Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or the integer 1; and R^9 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group as herein described in relation to Cy^1.

When Alk^4 is present as an aliphatic or heteroaliphatic chain it may be for example any aliphatic or heteroaliphatic chain as hereinbefore described for Alk^1.

Optionally substituted aromatic groups represented by the groups Cy^1 include for example monocyclic or bicyclic fused ring C_{6-12}aromatic groups, such as phenyl, 1- or 2-napthyl, 1- or 2-tetrahydronapthyl, indanyl or indenyl groups.

Heteroaromatic groups represented by the groups Cy^1 include for example C_{1-9}heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the

heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, [2,3-dihydro]benzothienyl, benzotriazolyl, indolyl, indolinyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-c]pyrimidinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, imidyl, e.g. succinimidyl, phthalimidyl or naphthalimidyl such as 1,8-naphthalimidyl, pyrazolo[4,3-d]pyrimidinyl, furo[3,2-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyrrolo[3,2-d]pyrimidinyl, pyrazolo[3,2-b]pyridinyl, furo[3,2-b]pyridinyl, thieno[3,2-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, thiazolo[3,2-a]pyyridinyl, pyrido[1,2-a]pyrimidinyl, tetrahydroimidazo[1,2-a]pyrimidinyl and dihydroimidazo[1,2-a]pyrimidinyl groups.

Optional substituents which may be present on aromatic or heteroaromatic groups represented by the group Cy^1 include one, two, three or more

substituents, each selected from an atom or group R^{10} in which R^{10} is R^{10a} or $-L^6Alk^5(R^{10a})_r$, where R^{10a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{11}$ [where R^{11} is an $-L^6Alk^3(R^{10a})_r$, aryl or heteroaryl group], $-CSR^{11}$, $-SO_3H$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-SO_2NH_2$, $-SO_2NHR^{11}$, $-SO_2N(R^{11})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{11}$, $-CSNHR^{11}$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-N(R^{12})SO_2R^{11}$ [where R^{12} is a hydrogen atom or a straight or branched alkyl group], $-N(SO_2R^{11})_2$, $-N(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{11}$, $-N(R^{12})SO_2N(R^{11})_2$, $-N(R^{12})COR^{11}$, $-N(R^{12})CONH_2$, $-N(R^{12})CONHR^{11}$, $-N(R^{12})CON(R^{11})_2$, $-N(R^{12})CSNH_2$, $-N(R^{12})CSNHR^{11}$, $-N(R^{12})CSN(R^{11})_2$, $-N(R^{12})CSR^{11}$, $-N(R^{12})C(O)OR^{11}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other –O- or -S- atoms or $-N(R^{12})-$, -C(O)- or –C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het$ [where -Het is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more other –O- or –S- atoms or $-N(R^{12})-$, -C(O)-, -S(O)- or $-S(O)_2-$ groups], -Het, $-CON(R^{12})Het$, $-CSN(R^{12})Het$, $-N(R^{12})CON(R^{12})Het$, $-N(R^{12})CSN(R^{12})Het$, $-N(R^{12})SO_2N(R^{12})Het$, aryl or heteroaryl groups; L^6 is a covalent bond or a linker atom or group as hereinbefore defined for L^2; Alk^5 is an optionally substituted straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three –O- or -S- atoms or $-S(O)_n-$ [where n is an integer 1 or 2] or $-N(R^{12})-$ e.g. $-N(CH_3)-$ groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

When in the group $-L^6Alk^5(R^{10a})_r$ r is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{10a} may be present on any suitable carbon atom in $-Alk^5$. Where more than one R^{10a} substituent is present these may be

the same or different and may be present on the same or different atom in $-Alk^5$. Clearly, when r is zero and no substituent R^{10a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^5 becomes an alkyl, alkenyl or alkynyl group.

When R^{10a} is a substituted amino group it may be for example a group $-NHR^{11}$ [where R^{11} is as defined above] or a group $-N(R^{11})_2$ wherein each R^{11} group is the same or different.

When R^{10a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{10a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{11}$ or a $-SR^{12}$ group respectively.

Esterified carboxyl groups represented by the group R^{10a} include groups of formula $-CO_2Alk^6$ wherein Alk^6 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^6 group include R^{10a} atoms and groups as described above.

When Alk^5 is present in or as a substituent it may be for example a $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-C(CH_3)_2CH_2-$, $-CH=CH-$, $-CH=CCH_2-$, $-CH_2C=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH_2-$, -CC-, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-CH_2CH_2CC-$ chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{12})-$, e.g. $-N(CH_3)-$ groups. The aliphatic chains represented by Alk^5 may be optionally substituted by one, two or three halogen atoms in addition to any R^{10a} groups that may be present.

Aryl or heteroaryl groups represented by the groups R^{10a} or R^{11} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Cy^1. The aromatic and heteroaromatic groups may be attached to the group Cy^1 in compounds of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

It will be appreciated that when $-NHet^1$ or –Het forms part of a substituent R^{10} the heteroatoms or heteroatom containing groups that may be present within the ring $-NHet^1$ or –Het take the place of carbon atoms within the parent carbocyclic ring.

Thus when $-NHet^1$ or –Het forms part of a substituent R^{10} each may be for example an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-NHet^1$ include those substituents described above when Cy^1 is a heterocycloaliphatic group.

Particularly useful atoms or groups represented by R^{10} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{3-7}cycloalkyl, e.g. cyclobutyl, cyclopentyl, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino, ethylamino, $-CH(CH_3)NH_2$ or $-C(CH_3)_2NH_2$, haloC_{1-6}alkylamino, e.g. fluoroC_{1-6}alkylamino,e.g. $-CH(CF_3)NH_2$ or $-C(CF_3)_2NH_2$, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^6$ [where Alk^6 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylamino-carbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethyl-aminocarbonyl, aminocarbonylamino, C_{1-}

$_6$alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylamino-carbonylamino, e.g. dimethylaminocarbonylamino or diethylamino-carbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylamino-carbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonyl-amino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonyl-amino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkyl-sulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethyl-aminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoyl-amino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethyl-amino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonyl-amino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxy-carbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridyl-methylthio or thiazolylmethylthio groups.

A further particularly useful group of substituents represented by R^{10} when present on aromatic or heteroaromatic groups includes substituents of formula –$L^6Alk^5R^{10a}$ where L^6 is preferably a covalent bond or an –O- or -S- atom or –$N(R^2)$-, -C(O)-, -C(O)O-, -O-C(O)-, -$N(R^2)$CO-, -CON(R^2)- or –$N(R^2)S(O)_2$-

group, Alk^5 is an optionally substituted C_{1-6}alkyl group optionally interrupted by one or two –O- or –S- atoms or $-N(R^{12})$-, -C(O)-, -C(S)-, $-CON(R^{12})$- or $-N(R^{12})CO$- groups and R^{10a} is an optionally substituted Het group as herein defined or an optionally substituted heteroaromatic group as hereinbefore described in relation to Cy^1.

Where desired, two R^{10} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group represented by the group Cy^1.

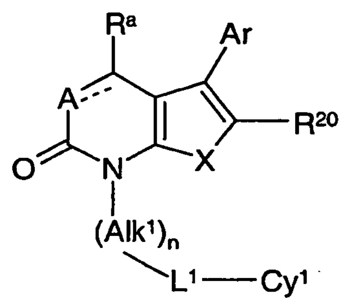
When in compounds of formula (1a) X is a substituted –N- atom or in compounds of formulae (1a) or (1b) Y is a substituted C atom the substituents which may be present on the N or C atom include those R^{10} atoms and groups as hereinbefore defined.

When Ar is present in compounds of formulae (1a) or (1b) as an optionally substituted aromatic or heteroaromatic group it may be any such group as hereinbefore described for Cy^1. Optional substituents which may be present include those R^{10} atoms and groups as described in relation to Cy^1 aromatic and heteroaromatic groups.

One useful group of compounds according to the invention is that where Y is a CH group or a substituted C atom where the substituent on the C atom may in general be any R^{10} atom or group as hereinbefore described or in particular a R^{20} group as hereinafter defined.

A particularly useful group of compounds according to the invention is represented by the compounds of formula (1a).

An especially useful group of compounds according to the invention has the formula (2a):



(2a)

in which

R^{20} is a hydrogen atom or an atom or group R^{10} as hereinbefore defined;

the dashed line, A, R^a, Alk^1, n, L^1, Cy^1, X and Ar are as generally and specifically defined previously;

and the salts, solvates, hydrates and N-oxides thereof.

In general in compounds of formula (1a), (1b) and (2a) R^a is preferably a hydrogen atom or a C_{1-4}alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. Most preferably R^a is a methyl group or most especially a hydrogen atom.

In one particularly preferred class of compounds of formula (1a), (1b) and (2a) the dashed line represents a bond and A is a -C(R^b)= group. In this class of compounds R^b is preferably a C_{1-4}alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. Most preferably R^b is a methyl group or most especially a hydrogen atom.

In one preferred class of compounds of formulae (1a) and (2a) X is a –O- or –S- atom, most preferably a –S- atom.

In another preferred group of compounds of formulae (1a), (1b) and (2a) n is zero.

In another preferred group of compounds of formulae (1a), (1b) and (2a) n is the integer 1 and Alk^1 is preferably an optionally substituted C_{1-6}alkylene chain, especially an optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ chain, most especially a $-CH_2-$ or $-CH_2CH_2-$ chain.

In compounds of formula (2a) and in general in compounds of the invention L^1 is preferably a covalent bond or an –O- or –S- atom or an $-N(R^2)-$, especially –NH- or $-N(CH_3)-$, -C(O)-, -C(S)-, -S(O)- or $-S(O)_2-$ group. Most preferably L^1 is a covalent bond or an –O- or –S- atom or –NH- group. L^1 is most especially preferably is a covalent bond.

In compounds of formula (2a) and in general in compounds of the invention Cy^1 is preferably an optionally substituted cycloaliphatic, aromatic or heteroaromatic group as hereinbefore generally and particularly defined.

Particularly preferred Cy^1 optionally substituted cycloaliphatic groups include optionally substituted C_{3-7}cycloalkyl groups, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups.

Particularly preferred optional substituents which may be present on Cy^1 optionally substituted cycloaliphatic groups include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl groups, especially C_{1-3}alkyl groups, most especially a methyl group, or a haloC_{1-6}alkyl group, especially a

fluoroC_{1-6}alkyl group, most especially a $-CF_3$ group, or a C_{1-6}alkoxy, especially methoxy, ethoxy, propxy or i-propoxy group, or a haloC_{1-6}alkoxy, especially a fluoroC_{1-6}alkoxy, most especially a $-OCF_3$ group, or a cyano (-CN), esterified carboxyl, especially $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-C(O)R^6$, especially $-C(O)CH_3$, or $-N(R^6)C(O)R^7$, especially $-NHCOCH_3$ group.

Particularly preferred Cy^1 aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

Particularly preferred optional substituents which may be present on Cy^1 aromatic or heteroaromatic groups include atoms or groups $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl groups, especially C_{1-3}alkyl groups, most especially a methyl group, or a haloC_{1-6}alkyl group, especially a fluoroC_{1-6}alkyl group, most especially a $-CF_3$ group, or a C_{1-6}alkoxy, especially methoxy, ethoxy, propxy or i-propoxy group, or a haloC_{1-6}alkoxy, especially a fluoroC_{1-6}alkoxy, most especially a $-OCF_3$ group, or a cyano (-CN), carboxyl ($-CO_2H$), esterified carboxyl ($-CO_2Alk^6$), especially $-CO_2CH_3$, $-CO_2CH_2CH_3$, or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-COR^{11}$, especially $-COCH_3$, or $-N(R^{12})COR^{11}$, especially $-NHCOCH_3$ group.

Further preferred optional substituents which may be present on Cy^1 aromatic or heteroaromatic groups include groups of formula $-L^6Alk^5(R^{10a})_r$ in which r is the integer 1, L^6 is a covalent bond or an –O- or –S- atom or a –N(R^2)-, especially –NH- or –N(CH_3)-, -C(O)-, -C(S)-, -C(O)O-, -OC(O)-, -N(R^2)CO-, especially –NHCO-, or –CON(R^2)-, especially –CHNH-group, Alk^5 is a C_{1-6}alkyl chain, especially a –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$- or –$CH_2CH_2CH_2CH_2$- chain and R^{10a} is a substituted hydroxyl group, especially a –OCH_3, -OCH_2CH_3 or –$OCH(CH_3)_2$ group or a substituted amino group, especially a –$N(CH_3)_2$ or –$N(CH_2CH_3)_2$ group or a –Het group, especially an optionally substituted monocyclic C_{5-7}carbocyclic group containing one, two or three –O-, -S-, -N(R^{12})-, especially –NH- or –N(CH_3)-or –C(O)- groups within the ring structure as previously described, most especially an optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. N-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group or R^{10a} is an optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, such as optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, triazinyl, pyridazinyl, or pyrazinyl group. Particularly preferred optional substituents on the –Het groups just described include hydroxyl (-OH) and carboxyl (-CO_2H) groups or those preferred optional substituents just described in relation to the group Cy^1.

In one preferred class of compounds of formula (2a) R^{20} is an atom or group –R^{10a} or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Preferably R^{20} is a preferred atom or group as just defined for Cy^1. In one particularly preferred class of compounds of formula (2a) R^{20} is a hydrogen atom or a carboxyl (-CO_2H), esterified carboxyl (-CO_2Alk^6), especially -CO_2CH_3, -$CO_2CH_2CH_3$, or -$CO_2C(CH_3)_3$, -CN, -NH_2, -$CONH_2$, -CONHR^{11}, -N(R^{12})SO_2R^{11}, -N(R^{12})C(O)OR^{11} or –SO_2R^{11} group.

In one particularly preferred group of compounds of formula (1), (1a) and (2a) Cy^1 is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three optional substituents where at least one, and preferably two optional substituents are located *ortho* to the bond joining Cy^1 to the remainder of the compound of formula (1), (1a) or (2a). Particularly preferred *ortho* substituents include halogen atoms, especially fluorine or chlorine atoms, or C_{1-3}alkyl groups, especially methyl groups, C_{1-3}alkoxy groups, especially methoxy, haloC_{1-3}alkyl groups, especially $-CF_3$, haloC_{1-3}alkoxy groups, especially $-OCF_3$, or cyano (-CN), groups. In this class of compounds a second or third optional substituent when present in a position other than the *ortho* positions of the ring Cy^1 may be preferably an atom or group $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as herein generally and particularly described.

Particularly preferred Ar aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

Particularly preferred optional substituents which may be present on Ar aromatic or heteroaromatic groups include atoms or groups $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl groups, especially C_{1-3}alkyl groups, most especially a methyl group, or a haloC_{1-6}alkyl group, especially a fluoroC_{1-6}alkyl group, most especially a $-CF_3$ group, or a C_{1-6}alkoxy, especially methoxy, ethoxy, propxy or i-propoxy

group, or a haloC_{1-6}alkoxy, especially a fluoroC_{1-6}alkoxy, most especially a $-OCF_3$ group, or a cyano (-CN), esterified carboxyl, especially $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-COR^{11}$, especially $-COCH_3$, or $-N(R^{12})COR^{11}$, especially $-NHCOCH_3$ group.

In one particularly preferred class of compounds of formula (2a) the dashed line is present, A is a –CH= group, R^a is a hydrogen atom and X is a –S- atom.

A further particularly useful class of compounds according to the invention has the formula (1b) in which the dashed line is present, A is a –CH= group, R^a, Ar, Alk^1, n and L^1 are as defined for formula (1b), each Y is independently a CH group or substituted C atom and Cy^1 is an optionally substituted aromatic or heteroaromatic group

Particularly useful compounds of the invention include:

Ethyl 6-oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 7-cyclopropylmethyl-6-oxo-3-phenyl -6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 6-oxo-3-phenyl-7-(3-thienyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(4-fluorophenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(2-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 6-oxo-7-phenyl-3-(4-tolyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

Ethyl 3-(3-methoxyphenyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

6-Oxo-3,7-diphenyl-*N*-(2-piperidinoethyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide;

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile;

3,7-Diphenylthieno[2,3-*b*]pyridin-6(7*H*)-one;

Ethyl 3-(2,4-difluorophenyl)-7-[4-(4-methylpiperazin-1-yl)phenyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

1,4-Diphenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one;

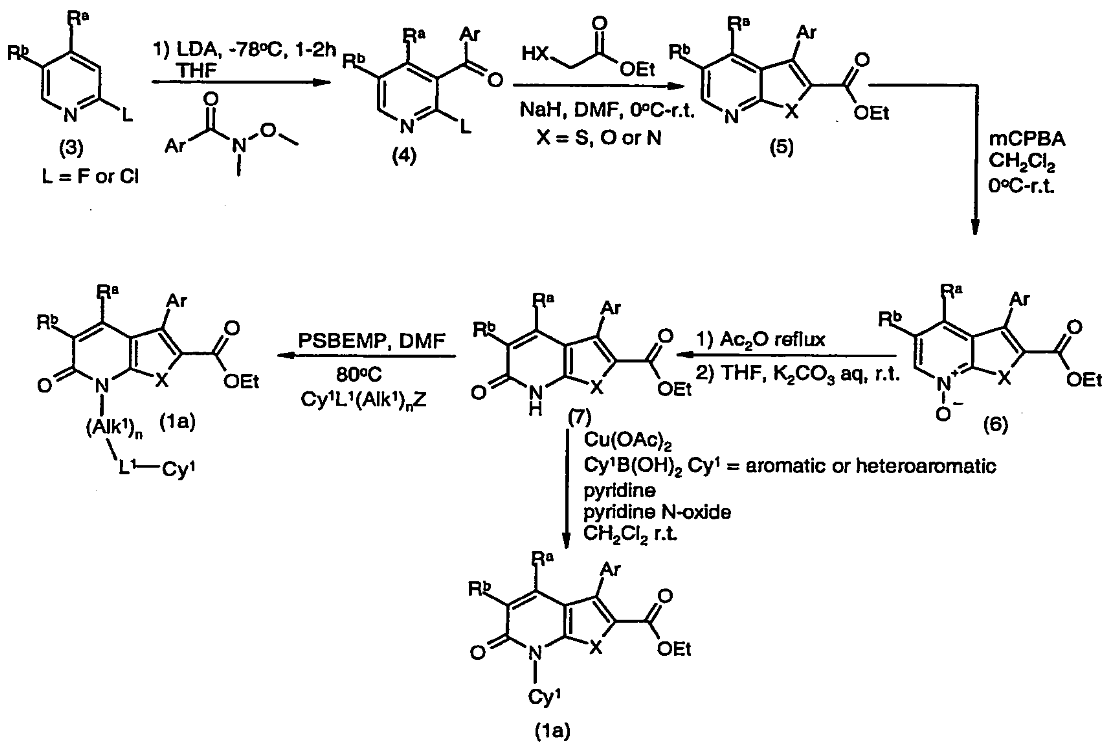
Ethyl 7-(2-chlorophenyl)-6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate;

and the salts, solvates, hydrates and N-oxides thereof.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, Cy^1, Alk^1, n, L^1, R^a, R^b, R^c, A, X and Y when used in the formulae depicted are to be understood to represent those groups described above in relation to formulae (1a) and (1b) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1a) or (1b) but clearly the description applies equally to the preparation of compounds of formula (2a).

Thus according to a further aspect of the invention a compound of formula (1a) in which Y is a substituted e.g. $-CO_2CH_2CH_3$ substituted C atom may be prepared according to the reactions set out in Scheme 1:

Scheme 1

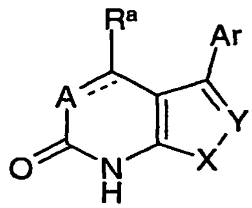


Thus a compound of formula (1a) in which Y is a substituted C atom may be prepared by reaction of a compound of formula (7) with an alkylating agent of formula $Cy^1L^1(Alk^1)_nZ$, where Z is a leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy e.g. phenylsulphonyloxy group.

The reaction may be performed in the presence of a solvent, for example a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an inorganic base such as sodium hydride, or an organic base such as an organic amine, e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene or a resin bound organic amine such as resin bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP), at an elevated temperature, for example 80 to 100ºC.

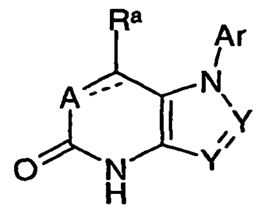
In a further aspect of the invention a compound of formula (1a) in which, for example, L^1 is a covalent bond and n is zero may be prepared by the reaction of a compound of formula (7) with a boronic acid of formula $Cy^1B(OH)_2$. The reaction may be performed in an organic solvent, for example a halogenated hydrocarbon such as dichloromethane or dichloroethane in the presence of a copper reagent, for example a copper (II) reagent such as copper (II) acetate, optionally in the presence of an oxidant, for example 2,2,6,6-tetramethyl-1-piperidinyloxy or pyridine-N-oxide, optionally in the presence of a base, for example an organic amine such as an alkylamine, e.g. triethylamine or an aromatic amine, e.g. pyridine at a temperature from around ambient to the reflux temperature [see for example Chan, D.T. *et al* Tetrahedron Letters, 1998, 2933; Lam, P.Y.S. *et al*, Tetrahedron Letters, 2001, 3415]

Clearly the reactions just described may be used to prepare other compounds of the invention starting from intermediates of formula (7a) or (7b):



(7a)

or



(7b)

for instance compounds of formula (7a) in which Y is a CH group.

Intermediates pyridinones of formula (7) may be prepared from pyridine N-oxides of formula (6) by sequential reaction with an anhydride, for example acetic anhydride at an elevated temperature, for example the reflux temperature followed by reaction with an inorganic base, for example a carbonate such as aqueous potassium carbonate in a solvent such as an ether for example a cyclic ether e.g. tetrahydrofuran at around ambient temperature.

Pyridine N-oxides of formula (6) may be formed from pyridines of formula (5) by standard methods of formation of N-oxides as described hereinafter.

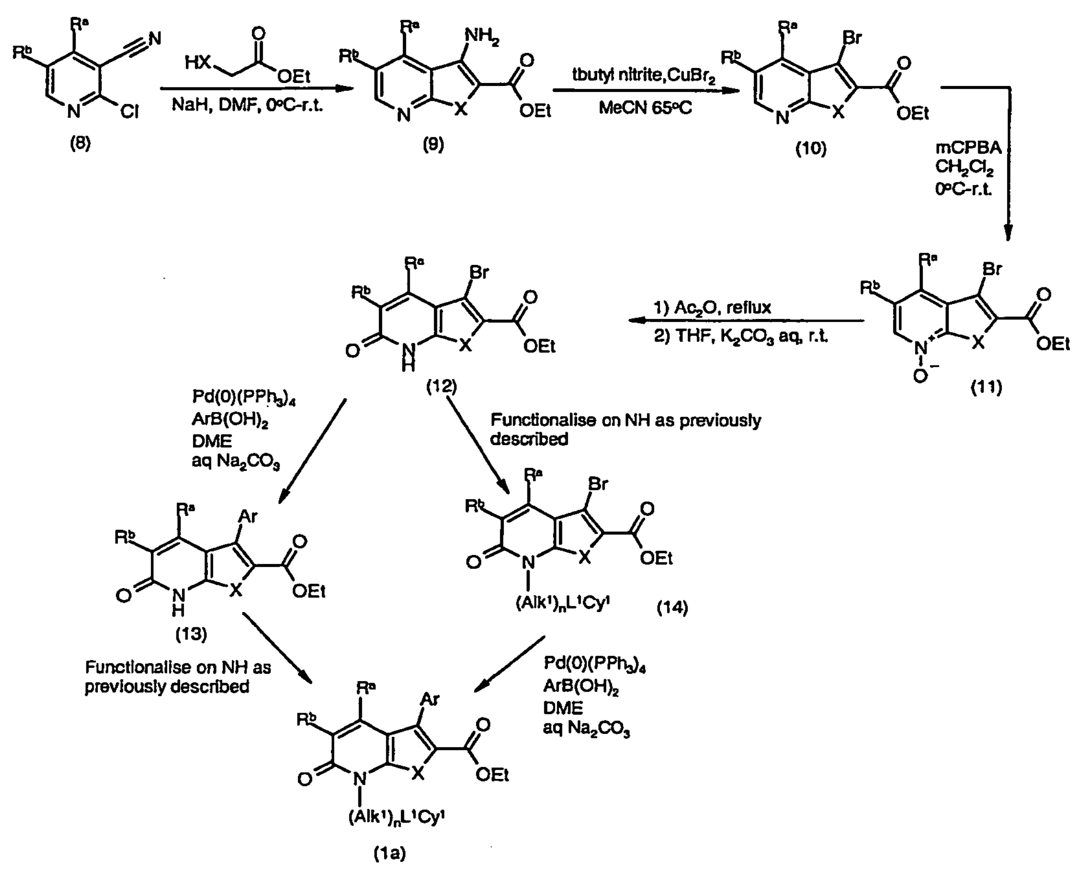
Pyridines of formula (5) may be formed from 2-halopyridyl-(hetero)arylmethanones of formula (4) by reaction with a reagent of formula $HXCH_2CO_2R^{30}$ [where R^{30} is a C_{1-6}alkyl group such as a methyl or ethyl group]. The reaction may be performed in the presence of a solvent such as a substituted amide for example dimethylformamide or an ether e.g. a cyclic ether such as tetrahydrofuran in the presence of a base, for example an inorganic base such as a hydride e.g. sodium hydride or an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene or a trialkylamine such as triethylamine at a temperature between about 0ºC and ambient temperature.

2-Halopyridyl-(hetero)arylmethanones of formula (4) may be prepared from 2-halopyridines of formula (3) by reaction with a base, for example a strong

base such as lithium diisopropylamide or butyl lithium to form a 2-halopyridyl anion and quenching with a (hetero)aryl amide such as a Weinreb amide. The reaction may be performed in the presence of a solvent such as a substituted amide for example dimethylformamide or an ether e.g. a cyclic ether such as, at a temperature of around-78ºC.

According to another aspect of the invention further compounds of formula (1a) may be prepared according to the reactions set out in Scheme 2.

Scheme 2



Thus further compounds of formula (1a) may be prepared from intermediates of formula (13), and intermediates of formula (14) may be prepared from intermediates of formula (12), by functionalisation at the 6-membered ring nitrogen according to the methods as previously described for the conversion of compounds of formula (7) to compounds of formula (1a).

Further compounds of formula (1a) may also be prepared from halogen substituted e.g. bromine substituted intermediates of formula (14), and intermediates of formula (13) may be prepared from halogen substituted e.g. bromine substituted intermediates of formula (12) by reaction with a boronic acid of formula $ArB(OH)_2$. The reaction may be performed in a solvent such as an acyclic ether, for example ethylene glycol dimethyl ether or a cyclic ether, for example tetrahydrofuran or an aromatic hydrocarbon, for example toluene in the presence of an inorganic catalyst such as a palladium catalyst e.g. tetrakis(triphenylphosphine) palladium (0) in the presence of a base, for example an aqueous inorganic base such as aqueous sodium, potassium or caesium carbonate at an elevated temperature, for example around 80ºC.

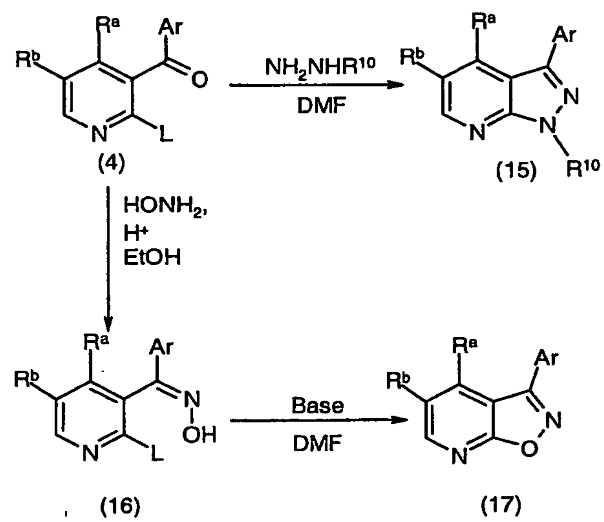
Pyridinones of formula (12) and pyridine N-oxides of formula (11) may be prepared by the methods as hereinbefore described.

Halides, for example bromides, of formula (10) may be prepared by such well known methods as for example the Sandmeyer reaction. Thus for example a bromide of formula (10) may be prepared by treatment of an aryl amine of formula (9) with an alkyl nitrite, for example t-butyl nitrite and a copper salt, for example copper (II) bromide in the presence of a solvent, for example a nitrile such as acetonitrile at a temperature from about 0º to around 65ºC.

Aryl amines of formula (9) may be prepared from halo nitriles of formula (8) by analogous methods to those used to prepare compounds of formula (5) as herein described.

Further 5-6 fused ring bicyclic heteroaromatic intermediates of formulae (15) and (17) may be prepared from intermediates of formula (4) by the methods shown in Scheme 3.

Scheme 3



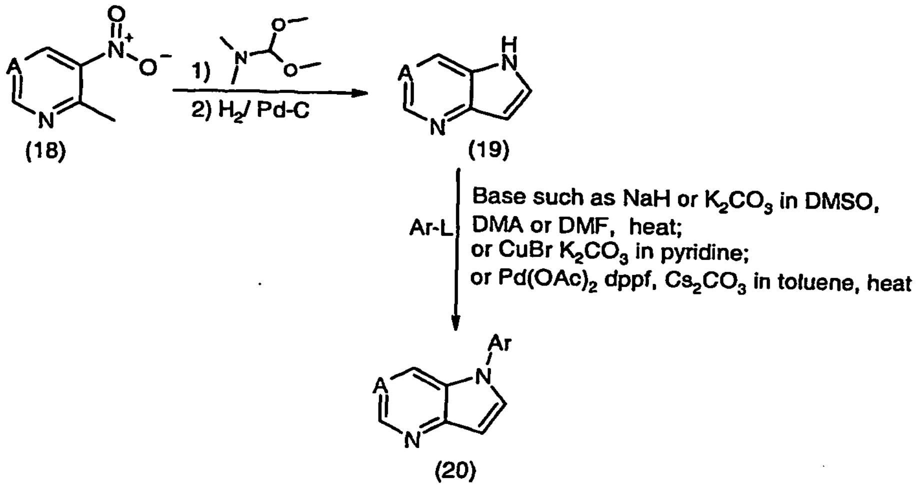
Thus pyrazolo[3,4-b]pyridines of formula (15) may be prepared by reaction of a 2-halopyridyl (or 2-halopyrimidinyl)-(hetero)arylmethanone of formula (4) with an optionally substituted hydrazine of formula $R^{10}NHNH_2$. The reaction may be performed in a solvent such as an amide for example a substituted

amide e.g. dimethylformamide, at an elevated temperature, for example from about 60ºC to the reflux temperature.

Similarly intermediate isoxazolo[3,4-b]pyridines of formula (17) may be prepared by reaction of a 2-halopyridyl (or 2-halopyrimidinyl)-(hetero)arylmethanone of formula (4) with hydroxylamine in the presence of an proton source for example hydrogen chloride in a solvent such as an alcohol, e.g. methanol or ethanol at a temperature from ambient to the reflux temperature to give an intermediate of formula (16) which may be cyclised to an intermediate of formula (17) by reaction with a base, for example an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBU) or an inorganic base such as a hydride e.g. sodium hydride in a solvent such as an amide for example a substituted amide e.g. dimethylformamide or an ether such as a cyclic ether e.g. tetrahydrofuran at a temperature from about 0ºC to ambient temperature.

Further pyrrolo[3,2-b]pyrimidine intermediates of formula (20) may be prepared from intermediates of formula (18) by the methods shown in Scheme 4.

<u>Scheme 4</u>



Thus a 1H-pyrrolo[3,2-b]pyridine (A=CH) or 1H-pyrrolo[3,2-b]pyrimidine (A=N) of formula (19) may be converted to an intermediate of formula (20) by reaction with a compound of formula Ar-L (in which L is a leaving group such as a halogen atom e.g. a fluorine, chlorine, bromine or iodine atom or a aryl sulfonate such as a triflate). The reaction may be performed in the presence of a base, for example a hydride such as sodium hydride or a carbonate such as potassium or caesium carbonate, in a solvent such as a sulfoxide e.g. dimethyl sulfoxide or an amide e.g. dimethylacetamide or dimethylformamide, at an elevated temperature e.g. from about 60ºC to 120ºC [according to the methods of Glamkowski, E. J. *et al*, J. Med. Chem., 1985, 28, 66 and Stabler, S. R. *et al*, Synth. Commun., 1994, 24, 123-29]. Alternatively the reaction may be performed with a compound of formula Ar-L (in which L is a leaving group such as a halogen atom e.g. a bromine atom or a aryl sulfonate such as a triflate) in the presence of a catalyst such as a copper catalyst e.g. copper (I) bromide in the presence of an inorganic base such as a carbonate e.g. potassium or caesium carbonate in a solvent such as an aromatic amine e.g. pyridine [according to the method of Ishii, H. *et al*, J. Chem. Soc. Perkin Trans. 1, 1989, 2407]. Alternatively the reaction may be performed with a

compound of formula Ar-L (in which L is a leaving group such as a halogen atom e.g. a bromine atom or a aryl sulfonate such as a triflate) in the presence of a catalyst such as a palladium catalyst e.g. palladium (ii) acetate in the presence of an iron catalyst e.g. 1,1'-bis(diphenylphosphino)ferrocene in a solvent such as an aromatic hydrocarbon e.g. toluene at an elevated temperature e.g. between 80ºC and the reflux temperature [according to the method of Mann, G. *et al*, J. Am. Chem. Soc., 1998, 120, 827-8].

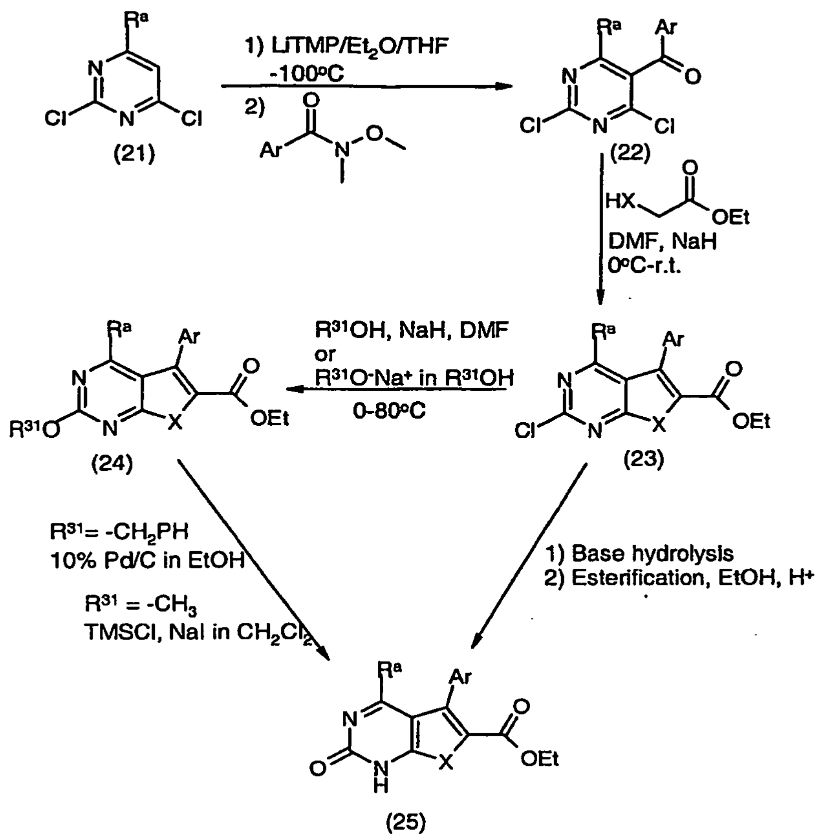
Intermediates of formula (19) may be formed from nitropyridines (A=CH) or nitropyrimidines (A=N) of formula (18) by sequential reaction with a dialkoxymethyl-dimethyl-amine such as dimethoxymethyl-dimethyl-amine followed by catalytic reduction with a palladium catalyst such as palladium on carbon [according to the method of Mahadevan, I. et al, J. Heterocyclic Chem., 1992, 29, 359-67].

Further 5-6 fused ring bicyclic heteroaromatic intermediates for use in the preparation of compounds of formula (1a) and (1b) may be prepared according to the methods of Japanese Patent Application JP9059276.

Such 5-6 fused ring bicyclic heteroaromatic intermediates of formula (15), (17), (19) and (20) as just described may be converted into further compounds of the invention by the particular methods as described above and general methods described below.

Further compounds of the invention in which A is a –N= atom may be prepared according to the methods shown in Scheme 5.

Scheme 5



Thus an intermediate of formula (25) may be converted to a compound of the invention according to the methods as herein described for the conversion of compounds of formula (7) to compounds of formula (1a).

Intermediates of formula (25) may be prepared from intermediates of formula (24) by cleavage of an ether group. Thus when R^{31} is a benzyl group it may be cleaved by such well known methods as catalytic reduction with hydrogen gas in the presence of a catalyst such as a palladium catalyst e.g. palladium on charcoal. When R^{31} is an alkyl ether, e.g. a methyl ether it may be cleaved by reaction with a trialkylsilyl halide such as trimethylsilyl chloride, optionally in the presence of an inorganic halide such as sodium iodide in a solvent such as a halogenated hydrocarbon e.g. dichloromethane or in a nitrile e.g.

acetonitrile [according to the methods of Kundu, N. G. *et al*, J. Chem. Soc. Perkin Trans. I, 1990, 1822].

Intermediates of formula (25) may also be prepared from intermediates of formula (23) sequential by base hydrolysis, for example soudium or potassium hydroxide hydrolysis in a solvent such as an alcohol, e.g. methanol or ethanol at an elevated temperature, e.g. the reflux temperture, followed by re-esterification by reaction with an acidified alcohol, e.g hydrogen chloride saturated ethanol at an elevated temperature, e.g. the reflux temperature.

Intermediates of formula (24) may be prepared from intermediates of formula (23) by reaction with an alkoxide, e.g. sodium methoxide or sodium benzyloxide in a solvent such as an alcohol, e.g. methanol or ethanol at a temperture between about 0ºC and the reflux temperature. Alternatively the reaction may be performed with an alcohol, e.g. methanol or benzyl alcohol in the presence of a strong base, e.g. a hydride such as sodium hydride in an inert solvent such as an amide, e.g. dimethylformamide at a temperature between about 0ºC and 80ºC

Intermediates of formula (23) may be formed from intermediates of formula (22) in a similar manner to that described for the preparation of intermediates of formula (5) form intermediates of formula (4).

Intermediates of formula (22) may be formed from intermediates of formula (21) by reaction with a strong base, e.g. lithium tetramethylpiperidine (LiTMP) in a solvent or mixture of solvents, for example an ether such as diethyl ether of tetrahydrofuran or a mixture thereof at a low temperature, e.g. around -100ºC to form a lithium anion [according to the methods of Queguiner *et al*, J. Het. Chem. 1990, 27, 1377 and Mattson *et al*, J. Org. Chem. 1990, 55, 3410]

which may be further reacted with a Weinreb amide at a temperature from about -78ºC to ambient temperature.

As an alternative a lithium anion as just described may be reacted with an aldehyde of formula ArCHO under the reaction conditions just described to give an intermediate alcohol which may be oxidised give an intermediate of formula (22) by such well known methods as manganese dioxide in a solvent, e.g. a halogenated hydrocarbon such as dichloromethane.

Compounds of the invention and intermediates thereto where A represents a $-N(R^b)-$ or $-C(R^b)(R^c)-$ group may be generated from compounds of the invention or intermediates thereto where A represents a $-N=$ or $-C(R^b)=$ group by reduction, for instance by catalytic hydrogenation using a metal catalyst such as palladium on charcoal in the presence of hydrogen gas at an elevated pressure in a solvent such as an alcohol, e.g. ethanol optionally at an elevated temperaure e.g. between 40 and 60º.

Where in the general processes described above intermediates such as alkylating agents of formula $Cy^1L^1(Alk^1)_nZ$, amides of formula ArC(O)N(OMe)Me, reagents of formula $HXCH_2CO2Et$ and nitroaromatics of formula (18) and any other intermediates required in the synthesis of compounds of the invention are not available commercially or known in the literature, they may be readily obtained from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other intermediates and in particular compounds of formulae (1a) and

(1b) where appropriate functional groups exist in these compounds. Particular examples of such methods are given in the Examples hereinafter.

Thus for example aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile, a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile, an alcohol group may be introduced by using an aldehyde as electrophile and an acid may be introduced by using carbon dioxide as electrophile. Aromatic acids of formula $ArCO_2H$ may also be generated by quenching Grignard reagents of formula ArMgHal with carbon dioxide.

Aromatic acids of formula $ArCO_2H$ generated by this method and acid containing compounds in general may be converted to activated derivatives, e.g. acid halides by reaction with a halogenating agent such as a thionyl halide e.g. thionyl chloride, a phosphorous trihalide such as phosphorous trichloride or a phosphorous pentahalide such as phosphorous pentachloride optionally in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to the reflux temperature, or may be converted into Weinreb amides of formula ArC(O)N(OMe)Me by conversion to the acid halide as just described and subsequent reaction with an amine of formula HN(OMe)Me or a salt thereof, optionally in the presence of a base such as an organic amine, e.g. triethylamine in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to ambient temperature.

Compounds of the invention and intermediates thereto such as compounds of formulae (5), (6), (7), (13) and (14) may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ group (where L^1 is a linker atom or group) may be treated with an alkylating agent Cy^1Z^2 in which Z^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^2H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with the alkylating agents just described but in which Z^2 is replaced by a -$C(O)Z^3$, $C(S)Z^3$, -$N(R^2)COZ^3$or -$N(R^2)C(S)Z^3$ group in which Z^3 is a leaving atom or group as described for Z^2. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which Z^2 is replaced by a -CO_2H group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [O-(7-azabenzo-triazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the

presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which Z^2 is replaced by a -S(O)Hal or -SO_2Hal group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a –L^2H group as defined above may be coupled with one of the alkylation agents just described but in which Z^2 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

Ester groups such as –CO_2Alk^6 and –CO_2R^4 in the compound of formula (1) and intermediates thereto may be converted to the corresponding acid [-CO_2H] by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^6 or R^4. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, -OR^6 [where R^6 represents an alkyl group such as methyl group] in compounds of formula (1) and intermediates thereto may be

cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{31}$ group (where R^{31} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [e.g. $-CO_2Alk^6$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSR^7$ or $-CSNHR^7$ group may be prepared by treating a corresponding compound containing a $-NHCOR^7$ or $-CONHR^7$ group with a thiation reagent, such as Lawesson's Reagent or P_2S_5, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium triacetoxyborohyride or sodium cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine ($-CH_2NH_2$) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as

carbon, or Raney® nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an alcohol e.g. methanol or ethanol, optionally in the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0ºC to the reflux temperature.

In another example, sulphur atoms in the compounds, for example when present in a group L^1 or L^2 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In a further example N-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70ºC to 80ºC, or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent,such as a halogenated hydrocarbon e.g. dichloromethane or an alcohol e.g. tert-butanol at a temperature from the ambient temperature to the reflux temperature.

In another example compounds of formula (12) may be converted to further compounds as formula (13) in which Ar is an optionally substituted aromatic or heteroaromatic group for use in the synthesis of for example compounds of formula (1), using such well know and commonly used palladium mediated reaction conditions as are to be found in the general reference texts *Rodd's Chemistry of Carbon Compounds*, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis,* Volumes 1-19 (John Wiley and Sons, 1999),

Comprehensive Heterocyclic Chemistry, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis*, Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's Comprehensive Organic Transformations* (VCH Publishers Inc., 1989) and *March's Advanced Organic Chemistry* (John Wiley and Sons, 5th Ed., 2001).

Salts of compounds of formula (1a) or (1b) may be prepared by reaction of compounds of formula (1a) or (1b) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1a) or (1b) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1a) or (1b) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1a) or (1b) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in ^{o}C.

The following abbreviations are used:

NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
MeOH - methanol;	BOC - butoxycarbonyl;
DCM - dichloromethane;	AcOH - acetic acid;
DIPEA - diisopropylethylamine;	EtOH - ethanol;
Pyr - pyridine;	Ar - aryl;
DMSO - dimethylsulphoxide;	iPr - isopropyl;
Et_2O - diethylether;	Me - methyl;
THF - tetrahydrofuran,	DMF - N,N-dimethylformamide;
MCPBA - 3-chloroperoxybenzoic acid	NBS - N-bromosuccinimide
FMOC - 9-fluorenylmethoxycarbonyl	r.t. – room temperature

DBU - 1,8-Diazabicyclo[5,4-0]undec-7-ene

EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

HOBT - 1-hydroxybenzotriazole hydrate

All NMRs were obtained either at 300MHz or 400MHz.

Compounds were named with the aid of either Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany or ACD Labs Name (v.5.0) supplied by Avanced Chemical Development, Toronto, Canada.

LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following following method: Phenomenex Luna 3µC_{18}(2) 50x4.6mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of 0.9mLmin^{-1}, column temperature 40°C.

Gradient:-	Time	%B
	Initial	5
	2.00	95
	3.00	95
	5.0	5
	5.5	end

Intermediate 1

3-Benzoyl-2-fluoropyridine

To a freshly prepared solution of lithium diisopropylamide (22mmol) in dry THF (20mL) under nitrogen and cooled to –78° was added a solution of 2-fluoropyridine (1.94g, 20mmol) in dry THF (10mL). The reaction was stirred for 2.5h at –78° before adding a solution of N-methoxy-N-methyl benzamide (3.47g, 21mmol) in THF (8mL). The reaction mixture was allowed to warm to room temperature over 1.5h and stir at room temperature for 1h. The reaction was quenched with water (50mL), extracted with EtOAc (2x50mL), the extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (5-20% EtOAc in isohexane) to give the title compound as a colourless oil (1.05g, 26%). δH ($CDCl_3$) 8.44 (1H, ddd, J 4.9, 2.0, 1.1Hz), 8.06 (1H, ddd, J 9.3, 7.4, 2.0Hz), 7.84 (2H, dm, J 8.4Hz), 7.66 (1H, tt, J 7.4, 1.3 Hz), 7.52 (2H, tm, J 7.8Hz), 7.38 (1H, ddd, J 6.8, 4.9, 1.9Hz). LCMS (ES^+) RT 3.27 minutes, 202 $(M+H)^+$

Intermediate 2

Ethyl 3-Phenylthieno[2,3-*b*]pyridine-2-carboxylate

To a solution of ethyl 2-mercaptoacetate (0.6mL, 5.5 mmol) in dry DMF (10mL) under nitrogen and cooled with an ice bath was added sodium hydride (220mg of 60% dispersion in oil, 5.75mmol). After hydrogen evolution had ceased the cooling bath was removed and the reaction stirred at room temperature for 30 mins. A solution of Intermediate 1 (920mg, 4.6mmol) in DMF (5mL) was added and the reaction stirred at room temperature for 3h. The reaction was quenched with water (50mL) and extracted with EtOAc (3x50mL). The combined EtOAc layers were washed with brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of the title compound and uncyclised ethyl 2-(3-benzoylpyridin-2-ylsulfanyl)acetate. This crude mixture was dissolved in EtOH (10mL) and sodium ethoxide (10mL of 0.5M solution in EtOH, 5.0mmol) added. The reaction was stirred at room temperature for 45 mins after which time complete conversion of uncyclised material to title compound was observed. The reaction was diluted with EtOAc (50mL), washed with water (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (10%EtOAc in isohexane) to give the title compound as a white solid (780mg, 60%). δH ($CDCl_3$) 8.63 (1H, dd, J 4.5, 1.4Hz), 7.78 (1H, dd, J 8.2, 1.5Hz), 7.41 (3H, m), 7.33-7.32 (2H, m), 7.24 (1H, dd, J 8.2, 4.6Hz), 4.18 (2H, q, J 7.1Hz), 1.15 (3H, t, J 7.1Hz) LCMS (ES^+) RT 3.90 minutes, 284 $(M+H)^+$.

Intermediate 3

Ethyl 3-phenylthieno[2,3-*b*]pyridine-2-carboxylate N-oxide

To a solution of Intermediate 2 in DCM (10mL) was added MCPBA (738mg of 60%w/w, 2.57mmol) and the reaction stirred at r.t. for 6h. The reaction mixture was diluted with DCM (20mL), washed with 2M NaOH (aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (80% EtOAc in isohexane – EtOAc) to give the title

compound as a white solid (670mg, 90%). δH ($CDCl_3$) 8.36 (1H, d, J 6.1 Hz), 7.55-7.49 (4H, m), 7.44-7.39 (2H, m), 7.26 (1H, dd, J 8.2, 6.2 Hz), 4.20 (2H, q, J 7.1 Hz), 1.16 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.18 minutes, 300 $(M+H)^+$

Intermediate 4

Ethyl 6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 3 (400mg, 1.34mmol) and acetic anhydride (20mL) was heated to reflux for 18h. The reaction mixture was concentrated *in vacuo* and the residue co-evapourated with toluene (4x20mL). The crude material was dissolved in THF (20mL) and treated with 10% aqueous K_2CO_3 (20mL). The reaction was stirred at room temperature for 18h and then extracted with EtOAc (3x25mL). The EtOAc extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (40-50% EtOAc in isohexane) to give the title compound as a white solid (193mg, 48%). δH ($CDCl_3$) 7.48 (1H, d, J 9.5Hz), 7.43-7.36 (3H, m), 7.31-7.28 (2H, m), 6.53 (1H, d, J 9.5Hz), 4.13 (2H, q, J 7.1Hz), 1.12 (3H, t, J 7.1Hz). LCMS (ES^+) RT 3.25 minutes, 322 ($(M+Na)^+$, 24%), 300 ($(M+H)^+$, 100%).

Intermediate 5

Ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of 2-chloro-3-cyanopyridine (330 g), ethyl 2-mercaptoacetate (361.2 g), sodium carbonate (265 g) and EtOH (1.2L) was heated to reflux for 4.5 hours. It was then cooled to ambient temperature, added to water (10L) and the addition was washed in with water (5L). The resulting slurry was stirred for 30 minutes and then it was filtered. The filter cake was washed with two portions of water (2 x 2.5L) and dried at the pump. The solids were then dried to constant weight under vacuum at 45° to yield the title compound as a brown solid (493.1 g, 93.2%). δH ($CDCl_3$) 8.68 (1H, dd, J 4.7, 1.2 Hz), 7.93 (1H, dd, J 8.5, 1.2 Hz), 7.29 (1H, dd, J 8.5, 4.7 Hz), 5.90 (2H, b), 4.38 (2H, q, J 7.0 Hz), 1.40 (3H, t, J 7.0 Hz). LCMS RT 2.9 minutes, 223 $(M+H)^+$

Intermediate 6

Ethyl 3-bromothieno[2,3-*b*]pyridine-2-carboxylate

Intermediate 5 (363.6g) was added in portions over two hours to a mixture of copper(II) bromide (403.3g), t-butyl nitrite (220.6 g) and acetonitrile (3.6L) stirred at a temperature of 20 to 25°. The mixture was stirred at 20° for 2 hours before it was slowly added to 2M HCl(aq) (4.2L). The reaction mixture slurry was filtered and the solids were washed with water (500 mL). The combined filtrate was extracted with EtOAc (8L), and the EtOAc solution was washed with 2M HCl(aq) (2.2L). The solids were dissolved in EtOAc (6L) and this solution was washed twice with 2M HCl(aq) (4.4L and 2.2L). The two EtOAc solutions were then combined and washed with 2M HCl(aq) (2.2L) and twice with water (2 x 2L). The EtOAc solution was then dried ($MgSO_4$), filtered and concentrated *in vacuo* at 40 mbar and 60° to give a solid residue. This was broken up and dried to constant weight under vacuum at 45° to yield the title compound as a brown solid (458.5g, 97.9%). δH (DMSO-d6) 8.89 (1H, d, J 4.7 Hz), 8.47 (1H, d, J 8.6 Hz), 7.71 (1H, dd, J 8.6, 4.7 Hz), 4.46 (2H, q, J 7.2 Hz), 1.40 (3H, t, J 7.2 Hz). LCMS RT 3.8 minutes, 288 $(M+H)^+$

Intermediate 7

Ethyl 3-Bromothieno[2,3-*b*]pyridine-2-carboxylate N-oxide

To a slurry of Intermediate 6 (214g, 0.747Mol) in DCM (2140mL) under nitrogen was added MCPBA (240g @ 70% = 168g, 0.97Mol) portion wise over 0.5h. The reaction was then stirred at r.t. for 18h. The reaction mixture was quenched with water (800mL) and pH adjusted to 8.5 with 10%w/v sodium carbonate solution (1250mL). The basic aqueous layer was removed and the organic layer washed with water until pH 7. The organic layer was concentrated *in vacuo* and the crude title product was recovered as a tan solid. The crude product was purified by slurrying in methyl *tert*-butyl ether

(600mL) for 1 hr at 0-5° to give the title compound (174g, 77%). δH ($CDCl_3$) 8.44 (1H, dd, J 6.2, 0.8 Hz), 7.87 (1H, dd, J 8.3, 0.8 Hz), 7.48 (1H, dd, J 8.3, 6.2 Hz), 4.49 (2H, q, J 7.1 Hz), 1.48 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.61 minutes, 302$(M)^+$

Intermediate 8

Ethyl 3-bromo-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 7 (500mg, 1.66mmol) and DMF (10mL) was set to stir at 0° under nitrogen. To this reaction mixture was added trifluoroacetic anhydride (3.49g, 2.36mL, 16.6mmol) in one portion via syringe. After stirring for 16 hours the volatiles were removed *in vacuo* and the residue co-evaporated with toluene (2x20mL). The crude material was then extracted with EtOAc (2x100mL). The EtOAc extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by a re-slurry in toluene (10mL) to give the title compound as a beige solid (260mg, 52%). δH (DMSO-d6) 12.20 (1H, brs), 7.75 (1H, d, J 9.0Hz), 6.50 (1H, d, J 9.0Hz), 4.15 (2H, q, J 7.1Hz), 1.12 (3H, t, J 7.1Hz). LCMS (ES^+) RT 2.86 minutes, 302 ($(M+H)^+$, 100%). MP = 261.7-268.1°C.

Intermediate 9

Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a 2 necked round bottomed flask was added in sequence Intermediate 8 (302mg, 1.00mmol), copper(II) acetate (278mg, 1.50mmol, 150mol%), phenylboronic acid (488mg, 4.00mmol), DCM (5mL) and pyridine (158mg, 2.00mmol). The reaction was stirred at room temperature for 18h with the exclusion of moisture. The reaction was then diluted with DCM (50mL), washed with 2M HCl(aq) (50mL), the aqueous was re-extracted with DCM (50mL). The combined organics were then washed with water (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by a

slurry in methanol (12mL), to give the title compound as a beige solid (270mg, 72%). δH ($CDCl_3$) 7.82 (1H, d, J 8.5Hz), 7.70-7.62 (3H, m), 7.54-7.42 (2H, m), 6.70 (1H, d, J 8.5Hz), 4.15 (2H, q, J 7.1Hz), 1.14 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.75 minutes, 378 $(M+H)^+$. MP = 201.6-206.0°C.

Intermediate 10

Ethyl 3-(4-fluorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 8 (241mg, 0.8mmol), tetrakis(triphenylphosphine)palladium(0) (92mg, 0.08mmol, 10mol%), 2M K_2CO_3 (aq) (0.8mL, 1.6mmol) and 4-fluorophenylboronic acid in ethylene glycol dimethyl ether (10mL) was heated to reflux under nitrogen for 20h. Solvent was removed *in vacuo* and the crude product purified by chromatography on silica (10% THF in DCM) to give the title compound as a white solid (210mg). LCMS (ES^+) RT 3.24 minutes, 318 $(M+H)^+$.

Intermediate 11

6-Oxo-3-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxamide

To a solution of Intermediate 4 (5.13g, 17 mmol) in 1:1 THF water (200mL) was added lithium hydroxide monohydrate (1.6g, 37.4mmol) and the reaction stirred at r.t. overnight. The reaction was incomplete at this time and was therefore concentrated on a rotary evaporator by approx. half and the reaction heated at 60° for 20h. Reaction showed complete conversion to the carboxylic acid at this time. The reaction was diluted with water (50mL) and 2M HCl(aq) added with stirring until a precipitate had formed (pH 1-2). The solid was filtered, washed with several portions of water and dried in a vacuum oven to afford 6-oxo-3-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylic acid as a solid (3.0g). LC RT 2.72 minutes. This compound was suspended in anhydrous DMF (30mL), 1,1'-carbonyldiimidazole (2.14g, 13.2 mmol) added and the reaction stirred for 30 mins. Ammonia (75mL of 25%

aqueous solution) was added and the reaction stirred at r.t. for 1h before being concentrated *in vacuo*. The resultant solid was suspended in 2M HCl(aq), collected by filtration and dried in a vacuum oven to give the title compound as a white solid (2.63g). δH (DMSO-d6) 7.63-7.49 (4H, m), 7.45-7.42 (2H, m), 6.51 (1H, d, J 9.2Hz), 6.28 (1H, bs). LCMS (ES^+) 271 $(M+H)^+$.

Intermediate 12

6-oxo-3-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

To a solution of Intermediate 11 (270mg, 1.0mmol) and pyridine (141μL, 1.0mmol) in dry DCM (10mL) was added trifluoroacetic anhydride (160μL, 2.0mmol) and the reaction stirred at r.t. for 16h. Solvent was removed *in vacuo* and the resultant solid suspended in water (30mL) and acidified with 2M HCl(aq) (10mL). The solid was collected by filtration, washed with water (25mL) and dried *in vacuo* to afford the title compound as a white solid (220mg, 87%). δH (DMSO-d6) 7.85 (1H, d, J 9.1Hz), 7.63-7.58 (5H, m), 6.69 (1H, d, J 9.1Hz). LCMS (ES^+) 253 $(M+H)^+$.

Intermediate 13

6-Oxo-3,7-diphenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-sulfonyl chloride

To a solution of the compound of Example 84 (675mg, 2.5mmol) in dry DCM (20mL) cooled to –78° was added chlorosulfonic acid (1.72g, 14.7mmol) over 5 mins. After 15 minutes reaction was removed from the cooling bath and stirred at r.t. for 1h. Reaction was poured onto ice-water and extracted with DCM. The combined DCM extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow solid (65mg).

Intermediate 14

Ethyl 3-(2,4-difluorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

The title compound was prepared from Intermediate 8 and 2,4-difluorophenylboronic acid following the analogous procedure described for Intermediate 10. This gave the title compound as a white solid LCMS (ES^+) 336 $(M+H)^+$.

Intermediate 15

1-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine

1*H*-Pyrrolo[3,2-*b*]pyridine (0.5g, 4.24mmol), phenylboronic acid (1.03g, 8.44mmol), copper(II) acetate (1.54g, 8.48mmol), and 4A molecular sieves (2g), were suspended in DCM (10mL). Triethylamine (1.19mL, 8.5mmol) and pyridine (0.7mL, 8.65mmol) were added and the reaction stirred at r.t. for three days. The reaction mixture was diluted with further DCM, filtered and concentrated *in vacuo*. Chromatography (silica, EtOAc) gave the title compound (325mg). δH ($CDCl_3$) 7.80 (1H, d, J 8.2Hz), 7.54-7.30 (7H, m), 7.15 (1H, brs), 6.88 (1H, brs). LCMS (ES^+) RT 1.20 minutes, 195 $(M+H)^+$.

Intermediate 16

1-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine 4-oxide

Intermediate 15 (307mg, 1.58mmol) was dissolved in DCM (5mL) and treated with MCPBA (356mg, 2.06mmol). After stirring for eighteen hours at r.t. the reaction was diluted with DCM, washed twice with 2M sodium hydroxide, dried (sodium sulphate) and concentrated *in vacuo* to give the title compound (285mg). δH ($CDCl_3$) 8.15 (1H, d, J 6.2Hz), 7.55-7.47 (2H, m), 7.42-7.37 (5H, m), 7.07, (1H, dd, J 0.7, 3.5Hz), 7.01 (1H, dd, J 6.2, 8.4Hz). LCMS (ES^+) RT 2.527 minutes, 211 $(M+H)^+$.

Intermediate 17

1-Phenyl-1,4-dihydro-pyrrolo[3,2-*b*]pyridin-5-one

Intermediate 16 (273mg, 1.3mmol) was dissolved in DMF (3mL) and treated at 0° with trifluoroacetic anhydride (1.8mL, 13mmol), was allowed to warm to r.t. and stir for two hours. The reaction was diluted with toluene and